UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

MISC 06 176 (NGG) (KAM)

UNIVERSITY OF PITTSBURGH, Plaintiff v. MARC H. HEDRICK, PROSPER BENHAIM, HERMANN PETER LORENZ, and MIN ZHU Defendants.	CASE NO: (Litigation pending in U.S. District Court, Central District of California – Case No. CV04-9014-CBM (AJWx))

NOTICE OF MOTION

PLEASE TAKE NOTICE THAT Plaintiff University of Pittsburgh by its attorneys Drinker Biddle and Reath LLP, upon the annexed Affidavit of George J. Awad and Memorandum of Law in Support of Motion to Compel, on a date and on a time to be set by the Court will move this Court for an Order pursuant to Rules 26, 37 and 45 of the Federal Rules of Civil Procedure, at the Courthouse, 225 Cadman Plaza East, Brooklyn, NY 11201 to compel responses to its subpoena on third-parties Olympus Corporation and Olympus America Inc.

Dated: New York, New York

April 12, 2006

Respectfully submitted,

By: Charles Donohue

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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

UNIVERSITY OF PITTSBURGH, Plaintiff v. MARC H. HEDRICK, PROSPER BENHAIM, HERMANN PETER LORENZ, and MIN ZHU Defendants.	CASE NO: (Litigation pending in U.S. District Court, Central District of California – Case No. CV04-9014-CBM (AJWx)) **AFFIDAVIT OF GEORGE J. AWAD IN SUPPORT OF MOTION TO COMPEL**

STATE OF PENNSYLVANIA)
) ss
COUNTY OF PHILADELPHIA)

GEORGE J. AWAD, being duly sworn, deposes and says:

1. I am a member of the Pennsylvania bar and an associate in the law firm of Drinker Biddle & Reath LLP, attorneys for Plaintiff University of Pittsburgh ("UPITT"). I represent UPITT in the above-captioned matter and am admitted *pro hac vice*. I make this affidavit in support of UPITT's motion to compel responses to its subpoena on third-parties Olympus Corporation and Olympus America Inc. Copies of UPITT's subpoena duces tecum and subpoena for oral testimony are annexed hereto as Exhibit A.

2. This suit was filed in the Central District of California and arose over a dispute regarding inventorship of US Patent 6,777,231 ("'231 Patent"), a copy of which is annexed hereto as Exhibit B.

3. UPITT asserts that Defendants Marc H. Hedrick, Hermann Peter Lorenz, Prosper Benhaim and Min Zhu are not the proper inventors of the '231 Patent. The Defendants have counter-claimed against the remaining named inventors -- Adam Katz,

Ramon Lull and William Futrell – claiming that they are not proper inventors of the '231 Patent.

4. Defendants assigned their rights to the '231 Patent to the Regents of the University of California ("UC"), which in turn licensed the patent to Cytori.

5. Olympus Corporation ("Olympus Corp."), formed the joint venture Olympus-Cytori Inc. ("Olympus-Cytori") with Cytori Therapeutics, Inc. ("Cytori").

6. Cytori, whose President is Defendant Marc Hedrick, has since licensed the '231 Patent to Olympus-Cytori as part of a $55 million transaction with Olympus Corp.

7. To the best of my knowledge and belief Olympus America Inc. is a division of the Olympus Corp. through which Olympus Corp. does business in the United States.

8. On February 9, 2006, UPITT served both a subpoena for oral testimony and a subpoena duces tecum directed to Olympus Corp. on Olympus America Inc., at 2 Corporate Center Drive, Melville, NY 11747-3157 which is in the Eastern District of New York. A copy of Olympus Corp.'s entity status report is annexed hereto as Exhibit C.

9. On February 22, 2006, Olympus Corp. served objections to the subpoenas (Exh. D).

10. During a meet and confer regarding various discovery disputes on March 13, 2006 between UPITT, Defendants and various third parties, including Cytori and Olympus-Cytori, UPITT agreed not to pursue discovery against Olympus until after Cytori produced documents under UPITT's subpoena. A copy of the March 14, 2006

letter from Ms. Doyle to Mr. Olson summarizing the meet and confer is annexed hereto as Exhibit E.

11. Cytori's production of documents was deficient and Olympus-Cytori and Olympus Corp. have failed to produce any documents.

12. Counsel for plaintiff University of Pittsburgh has made a reasonable effort to resolve the instant discovery dispute with the opposing attorneys on this motion. Those efforts have been unsuccessful as Olympus Corp. has failed to provide the requested discovery. A copy of the April 3, 2006 letter from Mr. DelMaster to Mr. Olson summarizing the meet and confer regarding the deficient production is annexed hereto as Exhibit F.

12. A detailed analysis of Olympus's failure to respond to the subpoena is set forth in the accompanying Memorandum of Law of Plaintiff in Support of its Motion to Compel Responses to its Subpoena Duces Tecum on Third Parties Olympus Corporation and Olympus America Inc. The following exhibits support that analysis:

a. Annexed hereto as Exhibit G is a copy of excerpts from the Calhoun Deposition Transcript.

b. Annexed hereto as Exhibit H is a copy of the Protective Order.

c. Annexed hereto as Exhibit I is a copy of excerpts from the Shih Rough Deposition Transcript.

George J. Awad

Sworn to before me this

11th day of April 2006

Glynnis V. Harp

Notary Public

NOTARIAL SEAL
GLYNNIS V HARP Notary Public
City of Philadelphia, Phila. County
My Commission Expires June 13, 2006

A

US006777231B1

(12) **United States Patent**
Katz et al.

(10) **Patent No.: US 6,777,231 B1**
(45) **Date of Patent: Aug. 17, 2004**

(54) **ADIPOSE-DERIVED STEM CELLS AND LATTICES**

(75) Inventors: **Adam J. Katz**, Charlottesville, VA (US); **Ramon Llull**, Mallorca (ES); **William J. Futrell**, Pittsburgh, PA (US); **Marc H. Hedrick**, Encino, CA (US); **Prosper Benhaim**, Los Angeles, CA (US); **Hermann Peter Lorenz**, Los Angeles, CA (US); **Min Zhu**, Los Angeles, CA (US)

(73) Assignee: **The Regents of the University of California**, Oakland, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/936,665**

(22) PCT Filed: **Mar. 10, 2000**

(86) PCT No.: **PCT/US00/06232**

§ 371 (c)(1),
(2), (4) Date: **Sep. 10, 2001**

(87) PCT Pub. No.: **WO00/53795**

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Related U.S. Application Data

(60) Provisional application No. 60/123,711, filed on Mar. 10, 1999, and provisional application No. 60/162,462, filed on Oct. 29, 1999.

(51) **Int. Cl.**[7] **C12N 5/00**; C12N 5/08

(52) **U.S. Cl.** **435/325**; 435/366

(58) **Field of Search** 435/325, 366

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(List continued on next page.)

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(57) **ABSTRACT**

The present invention provides adipose-derived stem cells and lattices. In one aspect, the present invention provides a lipo-derived stem cell substantially free of adipocytes and red blood cells and clonal populations of connective tissue stem cells. The cells can be employed, alone or within biologically-compatible compositions, to generate differentiated tissues and structures, both in vivo and in vitro. Additionally, the cells can be expanded and cultured to produce hormones and to provide conditioned culture media for supporting the growth and expansion of other cell populations. In another aspect, the present invention provides a lipo-derived lattice substantially devoid of cells, which includes extracellular matrix material from adipose tissue. The lattice can be used as a substrate to facilitate the growth and differentiation of cells, whether in vivo or in vitro, into anlagen or even mature tissues or structures.

10 Claims, No Drawings

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ADIPOSE-DERIVED STEM CELLS AND LATTICES

This application is a:: 371 of Application One:: PCT/US00/06232 Filing Date:: Mar. 10, 2000 Which is a::NON PROV. OF PROVISIONAL Application Two:: 60/123,711 Filing Date:: Mar. 10, 1999 And which is a:: NON PROV. OF PROVISIONAL Application Three:: 60/162,462 Filing Date:: Oct. 29, 1999

BACKGROUND OF THE INVENTION

In recent years, the identification of mesenchymal stem cells, chiefly obtained from bone marrow, has led to advances in tissue regrowth and differentiation. Such cells are pluripotent cells found in bone marrow and periosteum, and they are capable of differentiating into various mesenchymal or connective tissues. For example, such bone-marrow derived stem cells can be induced to develop into myocytes upon exposure to agents such as 5-azacytidine (Wakitani et al., *Muscle Nerve*, 18(12), 1417–26 (1995)). It has been suggested that such cells are useful for repair of tissues such as cartilage, fat, and bone (see, e.g., U.S. Pat. Nos. 5,908,784, 5,906,934, 5,827,740, 5,827,735), and that they also have applications through genetic modification (see, e.g., U.S. Pat. No. 5,591,625). While the identification of such cells has led to advances in tissue regrowth and differentiation, the use of such cells is hampered by several technical hurdles. One drawback to the use of such cells is that they are very rare (representing as few as 1/2,000,000 cells), making any process for obtaining and isolating them difficult and costly. Of course, bone marrow harvest is universally painful to the donor. Moreover, such cells are difficult to culture without inducing differentiation, unless specifically screened sera lots are used, adding further cost and labor to the use of such stem cells. Thus, there is a need for a more readily available source for pluripotent stem cells, particularly cells that can be cultured without the requirement for costly prescreening of culture materials.

Other advances in tissue engineering have shown that cells can be grown in specially-defined cultures to produce three-dimensional structures. Spacial definition typically is achieved by using various acellular lattices or matrices to support and guide cell growth and differentiation. While this technique is still in its infancy, experiments in animal models have demonstrated that it is possible to employ various acellular lattice materials to regenerate whole tissues (see, e.g., Probst et al. *BJU Int.*, 85(3), 362–7 (2000)). A suitable lattice material is secreted extracellular matrix material isolated from tumor cell lines (e.g, Engelbreth-Holm-Swarm tumor secreted matrix—"matrigel"). This material contains type IV collagen and growth factors, and provides an excellent substrate for cell growth (see, e.g., Vukicevic et al., *Exp. Cell Res*, 202(1), 1–8 (1992)). However, as this material also facilitates the malignant transformation of some cells (see, e.g., Fridman, et al., *Int. J. Cancer*, 51(5), 740–44 (1992)), it is not suitable for clinical application. While other artificial lattices have been developed, these can prove toxic either to cells or to patients when used in vivo. Accordingly, there remains a need for a lattice material suitable for use as a substrate in culturing and growing populations of cells.

BRIEF SUMMARY OF THE INVENTION

The present invention provides adipose-derived stem cells and lattices. In one aspect, the present invention provides a lipo-derived stem cell substantially free of adipocytes and red blood cells and clonal populations of connective tissue stem cells. The cells can be employed, alone or within biologically-compatible compositions, to generate differentiated tissues and structures, both in vivo and in vitro. Additionally, the cells can be expanded and cultured to produce hormones and to provide conditioned culture media for supporting the growth and expansion of other cell populations. In another aspect, the present invention provides a lipo-derived lattice substantially devoid of cells, which includes extracellular matrix material from adipose tissue. The lattice can be used as a substrate to facilitate the growth and differentiation of cells, whether in vivo or in vitro, into anlagen or even mature tissues or structures.

Considering how plentiful adipose tissue is, the inventive cells and lattice represent a ready source of pluripotent stem cells. Moreover, because the cells can be passaged in culture in an undifferentiated state under culture conditions not requiring prescreened lots of serum, the inventive cells can be maintained with considerably less expense than other types of stem cells. These and other advantages of the present invention, as well as additional inventive features, will be apparent from the accompanying drawings and in the following detailed descriptions.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the invention pertains to a lipo-derived stem cell. Preferably, the stem cell is substantially free of other cell types (e.g., adipocytes, red blood cells, other stromal cells, etc.) and extracellular matrix material; more preferably, the stem cell is completely free of such other cell types and matrix material. Preferably, the inventive cell is derived from the adipose tisue of a primate, and more preferably a higher primate (e.g, a baboon or ape). Typically, the inventive cell will be derived from human adipose tissue, using methods such as described herein.

While the inventive cell can be any type of stem cell, for use in tissue engineering, desirably the cell is of mesodermal origin. Typically such cells, when isolated, retain two or more mesodermal or mesenchymal developmental phenotypes (i.e., they are pluripotent). In particular, such cells generally have the capacity to develop into mesodermal tissues, such as mature adipose tissue, bone, various tissues of the heart (e.g., pericardium, epicardium, epimyocardium, myocardium, pericardium, valve tissue, etc.), dermal connective tissue, hemangial tissues (e.g., corpuscles, endocardium, vascular epithelium, etc.), muscle tissues (including skeletal muscles, cardiac muscles, smooth muscles, etc.), urogenital tissues (e.g., kidney, pronephros, meta- and meso-nephric ducts, metanephric diverticulum, ureters, renal pelvis, collecting tubules, epithelium of the female reproductive structures (particularly the oviducts, uterus, and vagina)), pleural and peritoneal tissues, viscera, mesodermal glandular tissues (e.g., adrenal cortex tissues), and stromal tissues (e.g., bone marrow). Of course, inasmuch as the cell can retain potential to develop into mature cells, it also can realize its developmental phenotypic potential by differentiating into an appropriate precursor cell (e.g., a preadipocyte, a premyocyte, a preosteocyte, etc.). Also, depending on the culture conditions, the cells can also exhibit developmental phenotypes such as embryonic, fetal, hematopoietic, neurogenic, or neuralgiagenic developmental phenotypes. In this sense, the inventive cell can have two or more developmental phenotypes such as adipogenic, chondrogenic, cardiogenic, dermatogenic, hematopoetic, hemangiogenic, myogenic, nephrogenic, neurogenic, neuralgiagenic, urogenitogenic, osteogenic, pericardiogenic,

peritoneogenic, pleurogenic, splanchogenic, and stromal developmental phenotypes. While such cells can retain two or more of these developmental phenotypes, preferably, such cells have three or more such developmental phenotypes (e.g, four or more mesodermal or mesenchymal developmental phenotypes), and some types of inventive stem cells have a potential to acquire any mesodermal phenotppe through the process of differentiation.

The inventive stem cell can be obtained from adipose tissue by any suitable method. A first step in any such method requires the isolation of adipose tissue from the source animal. The animal can be alive or dead, so long as adipose stromal cells within the animal are viable. Typically, human adipose stromal cells are obtained from living donors, using well-recognized protocols such as surgical or suction lipectomy. Indeed, as liposuction procedures are so common, liposuction effluent is a particularly preferred source from which the inventive cells can be derived.

However derived, the adipose tissue is processed to separate stem cells from the remainder of the material. In one protocol, the adipose tissue is washed with physiologically-compatible saline solution (e.g., phosphate buffered saline (PBS)) and then vigorously agitated and left to settle, a step that removes loose mater (e.g., damaged tissue, blood, erythrocytes, etc.) from the adipose tissue. Thus, the washing and settling steps generally are repeated until the supernatant is relatively clear of debris.

The remaining cells generally will be present in lumps of various size, and the protocol proceeds using steps gauged to degrade the gross structure while minimizing damage to the cells themselves. One method of achieving this end is to treat the washed lumps of cells with an enzyme that weakens or destroys bonds between cells (e.g., collagenase, dispase, trypsin, etc.). The amount and duration of such enzymatic treatment will vary, depending on the conditions employed, but the use of such enzymes is generally known in the art. Alternatively or in conjunction with such enzymatic treatment, the lumps of cells can be degraded using other treatments, such as mechanical agitation, sonic energy, thermal energy, etc. If degradation is accomplished by enzymatic methods, it is desirable to neutralize the enzyme following a suitable period, to minimize deleterious effects on the cells.

The degradation step typically produces a slurry or suspension of aggregated cells (generally liposomes) and a fluid fraction containing generally free stromal cells (e.g., red blood cells, smooth muscle cells, endothelial cells, fibroblast cells, and stem cells). The next stage in the separation process is to separate the aggregated cells from the stromal cells. This can be accomplished by centrifugation, which forces the stromal cells into a pellet covered by supernatant. The supernatant then can be discarded and the pellet suspended in a physiologically-compatible fluid. Moreover, the suspended cells typically include erythrocytes, and in most protocols it is desirable to lyse these. Methods for selectively lysing erythrocytes are known in the art, and any suitable protocol can be employed (e.g., incubation in a hyper- or hypotonic medium). Of course, if the erythrocytes are lysed, the remaining cells should then be separated from the lysate, for example by filtration or centrifugation. Of course, regardless of whether the erythrocytes are lysed, the suspended cells can be washed, re-centrifuged, and resuspended one or more successive times to achieve greater purity. Alternatively, the cells can be separated using a cell sorter or on the basis of cell size and granularity, stem cells being relatively small and agranular. Expression of telomerase can also serve as a stem cell-specific marker. They can also be separated immunohistochemically, for example, by panning or using magnetic beads. Any of the steps and procedures for isolating the inventive cells can be performed manually, if desired. Alteratively, the process of isolating such cells can be facilitated through a suitable device, many of which are known in the art (see, e.g., U.S. Pat. No. 5,786,207).

Following the final isolation and resuspension, the cells can be cultured and, if desired, assayed for number and viability to assess the yield. Desirably the cells can be cultured without differentiation using standard cell culture media (e.g, DMEM, typically supplemented with 5-15% (e.g., 10%) serum (e.g., fetal bovine serum, horse serum, etc.). Preferably, the cells can be passaged at least five times in such medium without differentiating, while still retaining their developmental phenotype, and more preferably, the cells can be passaged at least 10 times (e.g., at least 15 times or even at least 20 times) without losing developmental phenotype. Thus, culturing the cells of the present invention without inducing differentiation can be accomplished without specially screened lots of serum, as is generally the case for mesenchymal stem cells (e.g., derived from marrow). Methods for measuring viability and yield are known in the art (e.g., trypan blue exclusion).

Following isolation, the stem cells are further separated by phenotypic identification, to identify those cells that have two or more of the aforementioned developmental phenotypes. Typically, the stromal cells are plated at a desired density such as between about 100 cells/cm^2 to about 100,000 cells/cm^2 (such as about 500 cells/cm^2 to about 50,000 cells/cm^2, or, more particularly, between about 1,000 cells/cm^2 to about 20,000 cells/cm^2). If plated at lower densities (e.g., about 300 cells/cm^2), the cells can be more easily clonally isolated. For example, after a few days, cells plated at such densities will proliferate into a population.

Such cells and populations can be clonally expanded, if desired, using a suitable method for cloning cell populations. For example, a proliferated population of cells can be physically picked and seeded into a separate plate (or the well of a multi-well plate). Alternatively, the cells can be subcloned onto a multi-well plate at a statistical ratio for facilitating placing a single cell into each well (e.g., from about 0.1 to about 1 cell/well or even about 0.25 to about 0.5 cells/well, such as 0.5 cells/well). Of course, the cells can be cloned by plating them at low density (e.g, in a petri-dish or other suitable substrate) and isolating them from other cells using devices such as a cloning rings. Alternatively, where an irradiation source is available, clones can be obtained by permitting the cells to grow into a monolayer and then shielding one and irradiating the rest of cells within the monolayer. The surviving cell then will grow into a clonal population. While production of a clonal population can be expanded in any suitable culture medium, a preferred culture condition for cloning stem cells (such as the inventive stem cells or other stem cells) is about ⅔ F_{12}medium+20% serum (preferably fetal bovine serum) and about ⅓ standard medium that haw been conditioned with stromal cells (e.g., cells from the stromal vascular fraction of liposuction aspirate), the relative proportions being determined volumetrically).

In any event, whether clonal or not, the isolated cells can be cultured to a suitable point when their developmental phenotype can be assessed. As mentioned, the inventive cells have at least two of the aforementioned developmental phenotypes. Thus, one or more cells drawn from a given clone can be treated to ascertain whether it possesses such developmental potentials. One type of treatment is to culture the inventive cells in culture media that has been condi-

tioned by exposure to mature cells (or precursors thereof) of the respective type to be differentiated (e.g., media conditioned by exposure to myocytes can induce myogenic differentiation, media conditioned by exposure to heart valve cells can induce differentiation into heart valve tissue, etc.). Of course, defined media for inducing differentiation also can be employed. For example, adipogenic developmental phenotype can be assessed by exposing the cell to a medium that facilitates adipogenesis, e.g., containing a glucocorticoid (e.g., isobutyl-methylxanthine, dexamethasone, hydrocortisone, cortisone, etc.), insulin, a compound which elevates intracellular levels of cAMP (e.g., dibutyryl-cAMP, 8-CPT-cAMP (8-(4)chlorophenylthio)-adenosine 3', 5'cyclic monophosphate; 8-bromo-cAMP; dioctanoyl-cAMP, forskolin etc.), and/or a compound which inhibits degradation of cAMP (e.g., a phosphodiesterase inhibitor such as methyl isobutylxanthine, theophylline, caffeine, indomethacin, and the like). Thus, exposure of the stem cells to between about 1 μM and about 10 μM insulin in combination with about 10^{-9} M to about 10^{-6} M to (e.g., about 1 μM) dexamethasone can induce adipogenic differentiation. Such a medium also can include other agents, such as indomethicin (e.g., about 100 μM to about 200 μM, if desired, and preferably the medium is serum free. Osteogenic developmental phenotype can be assessed by exposing the cells to between about 10^{-7} M and about 10^{-9} M dexamethasone (e.g., about 1 μM) in combination with about 10 μM to about 50 μM ascorbate-2-phosphate and between about 10 nM and about 50 nM β-glycerophosphate, and the medium also can include serum (e.g., bovine serum, horse serum, etc.). Myogenic differentiation can be induced by exposing the cells to between about 10 μM and about 100 μM hydrocortisone, preferably in a serum-rich medium (e.g., containing between about 10% and about 20% serum (either bovine, horse, or a mixture thereof)). Chondrogenic differentiation can be induced by exposing the cells to between about 1 μM to about 10 μM insulin and between about 1 μM to about 10 μM transferrin, between about 1 ng/ml and 10 ng/ml transforming growth factor (TGF) β1, and between about 10 nM and about 50 nM ascorbate-2-phosphate (50 nM). For chondrogenic differentiation, preferably the cells are cultured in high density (e.g., at about several million cells/ml or using micromass culture techniques), and also in the presence of low amounts of serum (e.g., from about 1% to about 5%). The cells also can be induced to assume a developmentally more immature phenotype (e.g., a fetal or embryonic phenotype). Such induction is achieved upon exposure of the inventive cell to conditions that mimic those within fetuses and embryos. For example, the inventive cells or populations can be co-cultured with cells isolated from fetuses or embryos, or in the presence of fetal serum. Along these lines, the cells can be induced to differentiate into any of the aforementioned mesodermal lineages by co-culturing them with mature cells of the respective type, or precursors thereof. Thus, for example, myogenic differentiation can be induced by culturing the inventive cells with myocytes or precursors, and similar results can be achieved with respect to the other tissue types mentioned herein. Other methods of inducing differentiation are known in the art, and many of them can be employed, as appropriate.

After culturing the cells in the differentiating-inducing medium for a suitable time (e.g., several days to a week or more), the cells can be assayed to determine whether, in fact, they have differentiated to acquire physical qualities of a given type of cell. One measurement of differentiation per se is telomere length, undifferentiated stem cells having longer telomeres than differentiated cells; thus the cells can be assayed for the level of telomerase activity. Alternatively, RNA or proteins can be extracted from the cells and assayed (via Northern hybridization, rtPCR, Western blot analysis, etc.) for the presence of markers indicative of the desired phenotype. Of course, the cells can be assayed immunohistochemically or stained, using tissue-specific stains. Thus, for example, to assess adipogenic differentiation, the cells can be stained with fat-specific stains (e.g., oil red O, safarin red, sudan black, etc.) or probed to assess the presence of adipose-related factors (e.g., type IV collagen, PPAR-γ, adipsin, lipoprotein lipase, etc.). Similarly, osteogenesis can be assessed by staining the cells with bone-specific stains (e.g., alkaline phosphatase, von Kossa, etc.) or probed for the presence of bone-specific markers (e.g., osteocalcin, osteonectin, osteopontin, type I collagen, bone morphogenic proteins, cbfa, etc.). Myogensis can be assessed by identifying classical morphologic changes (e.g., polynucleated cells, syncitia formation, etc.), or assessed biochemically for the presence of muscle-specific factors (e.g., myo D, myosin heavy chain, NCAM, etc.). Chondrogenesis can be determined by staining the cells using cartallge-specific stains (e.g., alcian blue) or probing the cells for the expression/production of cartilage-specific molecules (e.g., sulfated glycosaminoglycans and proteoglycans (e.g., keratin, chondroitin, etc.) in the medium, type II collagen, etc.). Other methods of assessing developmental phenotype are known in the art, and any of them is appropriate. For example, the cells can be sorted by size and granularity. Also, the cells can be used to generate monoclonal antibodies, which can then be employed to assess whether they preferentially bind to a given cell type. Correlation of antigenicity can confirm that the stem cell has differentiated along a given developmental pathway.

While the cell can be solitary and isolated from other cells, preferably it is within a population of cells, and the invention provides a defined population including the inventive cell. In some embodiments, the population is heterogeneous. Thus, for example, the population can include support cells for supplying factors to the inventive cells. Of course, the inventive stem cells can themselves serve as support cells for culturing other types of cells (such as other types of stem cells, e.g., as neural stem cells (NSC), hematopoetic stem cells (HPC, particularly $CD34^+$ stem cells), embryonic stem cells (ESC) and mixtures thereof), and the population can include such cells. In other embodiments, the population is substantially homogeneous, consisting essentially of the inventive lipo-derived stem cells.

As the inventive cells can be cloned, a substantially homogeneous population containing them can be clonal. Indeed, the invention also pertains to any defined clonal cell population consisting essentially of mesodermal stem cells, connective tissue stem cell, or mixtures thereof. In this embodiment, the cells can be lipo-derived or derived from other mesodermal or connective cell tissues (e.g., bone marrow, muscle, etc.) using methods known in the art. After the isolation, the cells can be expanded clonally as described herein.

The inventive cells (and cell populations) can be employed for a variety of purposes. As mentioned, the cells can support the growth and expansion of other cell types, and the invention pertains to methods for accomplishing this. In one aspect, the invention pertains to a method of conditioning culture medium using the inventive stem cells and to conditioned medium produced by such a method. The medium becomes conditioned upon exposing a desired culture medium to the cells under conditions sufficient for the cells to condition it. Typically, the medium is used to

support the growth of the inventive cells, which secrete hormones, cell matrix material, and other factors into the medium. After a suitable period (e.g., one or a few days), the culture medium containing the secreted factors can be separated from the cells and stored for future use. Of course, the inventive cells and populations can be re-used successively to condition medium, as desired. In other applications (e.g., for co-culturing the inventive cells with other cell types), the cells can remain within the conditioned medium. Thus, the invention provides a conditioned medium obtained using this method, which either can contain the inventive cells or be substantially free of the inventive cells, as desired.

The conditioned medium can be used to support the growth and expansion of desired cell types, and the invention provides a method of culturing cells (particularly stem cells) using the conditioned medium. The method involves maintaining a desired cell in the conditioned medium under conditions for the cell to remain viable. The cell can be maintained under any suitable condition for culturing them, such as are known in the art. Desirably, the method permits successive rounds of mitotic division of the cell to form an expanded population. The exact conditions (e.g., temperature, CO_2 levels, agitation, presence of antibiotics, etc.) will depend on the other constituents of the medium and on the cell type. However, optimizing these parameters are within the ordinary skill in the art. In some embodiments, it is desirable for the medium to be substantially free of the lipo-derived cells employed to condition the medium as described herein. However, in other embodiments, it is desirable for the lipo-derived cells to remain in the conditioned medium and co-cultured with the cells of interest. Indeed, as the inventive lipo-derived cells can express cell-surface mediators of intercellular communication, it often is desirable for the inventive cells and the desired other cells to be co-cultured under conditions in which the two cell types are in contact. This can be achieved, for example, by seeding the cells as a heterogeneous population of cells onto a suitable culture substrate. Alternatively, the inventive lipo-derived cells can first be grown to confluence, which will serve as a substrate for the second desired cells to be cultured within the conditioned medium.

In another embodiment, the inventive lipo-derived cells can be genetically modified, e.g., to express exogenous genes or to repress the expression of endogenous genes, and the invention provides a method of genetically modifying such cells and populations. In accordance with this method, the cell is exposed to a gene transfer vector comprising a nucleic acid including a transgene, such that the nucleic acid is introduced into the cell under conditions appropriate for the transgene to be expressed within the cell. The transgene generally is an expression cassette, including a coding polynucleotide operably linked to a suitable promoter. The coding polynucleotide can encode a protein, or it can encode biologically active RNA (e.g., antisense RNA or a ribozyme). Thus, for example, the coding polynucleotide can encode a gene conferring resistance to a toxin, a hormone (such as peptide growth hormones, hormone releasing factors, sex hormones, adrenocorticotrophic hormones, cytokines (e.g., interferins, interleukins, lymphokines), etc.), a cell-surface-bound intracellular signaling moiety (e.g., cell adhesion molecules, hormone receptors, etc.), a factor promoting a given lineage of differentiation, etc. Of course, where it is desired to employ gene transfer technology to deliver a given transgene, its sequence will be known.

Within the expression cassette, the coding polynucleotide is operably linked to a suitable promoter. Examples of suitable promoters include prokaryotic promoters and viral promoters (e.g., retrovial ITRs, LTRs, immediate early viral promoters (IEp), such as herpesvirus IEp (e.g., ICP4-IEp and ICP0-IEp), cytomegalovirus (CMV) IEp, and other viral promoters, such as Rous Sarcoma Virus (RSV) promoters, and Murine Leukemia Virus (MLV) promoters). Other suitable promoters are eukaryotic promoters, such as enhancers (e.g., the rabbit β-globin regulatory elements), constitutively active promoters (e.g., the β-actin promoter, etc.), signal specific promoters (e.g., inducible promoters such as a promoter responsive to RU486, etc.), and tissue-specific promoters. It is well within the skill of the art to select a promoter suitable for driving gene expression in a predefined cellular context. The expression cassette can include more than one coding polynucleotide, and it can include other elements (e.g., polyadenylation sequences, sequences encoding a membrane-insertion signal or a secretion leader, ribosome entry sequences, transcriptional regulatory elements (e.g., enhancers, silencers, etc.), and the like), as desired.

The expression cassette containing the transgene should be incorporated into a genetic vector suitable for delivering the transgene to the cells. Depending on the desired end application, any such vector can be so employed to genetically modify the cells (e.g., plasmids, naked DNA, viruses such as adenovirus, adeno-associated virus, herpesviruses, lentiviruses, papillomaviruses, retroviruses, etc.). Any method of constructing the desired expression cassette within such vectors can be employed, many of which are well known in the art (e.g., direct cloning, homologous recombination, etc.). Of course, the choice of vector will largely determine the method used to introduce the vector into the cells (e.g., by protoplast fusion, calcium-phosphate precipitation, gene gun, electroporation, infection with viral vectors, etc.), which are generally known in the art.

The genetically altered cells can be employed as bioreactors for producing the product of the transgene. In other embodiments, the genetically modified cells are employed to deliver the transgene and its product to an animal. For example, the cells, once genetically modified, can be introduced into the animal under conditions sufficient for the transgene to be expressed in vivo.

In addition to serving as useful targets for genetic modification, many cells and populations of the present invention secrete hormones (e.g., cytokines, peptide or other (e.g., monobutyrin) growth factors, etc.). Some of the cells naturally secrete such hormones upon initial isolation, and other cells can be genetically modified to secrete hormones, as discussed herein. The cells of the present invention that secrete hormones can be used in a variety of contexts in vivo and in vitro. For example, such cells can be employed as bioreactors to provide a ready source of a given hormone, and the invention pertains to a method of obtaining hormones from such cells. In accordance with the method, the cells are cultured, under suitable conditions for them to secrete the hormone into the culture medium. After a suitable period of time, and preferably periodically, the medium is harvested and processed to isolate the hormone from the medium. Any standard method (e.g., gel or affinity chromatography, dialysis, lyophilization, etc.) can be used to purify the hormone from the medium, many of which are known in the art.

In other embodiments, cells (and populations) of the present invention secreting hormones can be employed as therapeutic agents. Generally, such methods involve transferring the cells to desired tissue, either in vitro (e.g., as a graft prior to implantation or engrafting) or in vivo, to

animal tissue directly. The cells can be transferred to the desired tissue by any method appropriate, which generally will vary according to the tissue type. For example, cells can be transferred to a graft by bathing the graft (or infusing it) with culture medium containing the cells. Alternatively, the cells can be seeded onto the desired site within the tissue to establish a population. Cells can be transferred to sites in vivo using devices such as catheters, trocars, cannulae, stents (which can be seeded with the cells), etc. For these applications, preferably the cell secretes a cytokine or growth hormone such as human growth factor, fibroblast growth factor, nerve growth factor, insulin-like growth factors, hemopoetic stem cell growth factors, members of the fibroblast growth factor family, members of the platelet-derived growth factor family, vascular and endothelial cell growth factors, members of the TGFb family (including bone morphogenic factor), or enzymes specific for congenital disorders (e.g., distrophin).

In one application, the invention provides a method of promoting the closure of a wound within a patient using such cells. In accordance with the method, the inventive cells secreting the hormone are transferred to the vicinity of a wound under conditions sufficient for the cell to produce the hormone. The presence of the hormone in the vicinity of the wound promotes closure of the wound. The method promotes closure of both external (e.g., surface) and internal wounds. Wounds to which the present inventive method is useful in promoting closure include, but are not limited to, abrasions, avulsions, blowing wounds, burn wounds, contusions, gunshot wounds, incised wounds, open wounds, penetrating wounds, perforating wounds, puncture wounds, seton wounds, stab wounds, surgical wounds, subcutaneous wounds, or tangential wounds. The method need not achieve complete healing or closure of the wound; it is sufficient for the method to promote any degree of wound closure. In this respect, the method can be employed alone or as an adjunct to other methods for healing wounded tissue.

Where the inventive cells secrete an angiogenic hormone (e.g., vascular growth factor, vascular and endothelial cell growth factor, etc.), they (as well as populations containing them) can be employed to induce angiogenesis within tissues. Thus, the invention provides a method of promoting neovascularization within tissue using such cells. In accordance with this method, the cell is introduced the desired tissue under conditions sufficient for the cell to produce the angiogenic hormone. The presence of the hormone within the tissue promotes neovascularization within the tissue.

Because the inventive stem cells have a developmental phenotype, they can be employed in tissue engineering. In this regard, the invention provides a method of producing animal matter comprising maintaining the inventive cells under conditions sufficient for them to expand and differentiate to form the desired matter. The matter can include mature tissues, or even whole organs, including tissue types into which the inventive cells can differentiate (as set forth herein). Typically, such matter will comprise adipose, cartilage, heart, dermal connective tissue, blood tissue, muscle, kidney, bone, pleural, splanchnic tissues, vascular tissues, and the like. More typically, the matter will comprise combinations of these tissue types (i.e., more than one tissue type). For example, the matter can comprise all or a portion of an animal organ (e.g., a heart, a kidney) or a limb (e.g., a leg, a wing, an arm, a hand, a foot, etc.). Of course, in as much as the cells can divide and differentiate to produce such structures, they can also form anlagen of such structures. At early stages, such anlagen can be cryopreserved for future generation of the desired mature structure or organ.

To produce such structures, the inventive cells and populations are maintained under conditions suitable for them to expand and divide to form the desired structures. In some applications, this is accomplished by transferring them to an animal (i.e., in vivo) typically at a sight at which the new matter is desired. Thus, for example, the invention can facilitate the regeneration of tissues (e.g., bone, muscle, cartilage, tendons, adipose, etc.) within an animal where the cells are implanted into such tissues. In other embodiments, and particularly to create anlagen, the cells can be induced to differentiate and expand into tissues in vitro. In such applications, the cells are cultured on substrates that facilitate formation into three-dimensional structures conducive for tissue development. Thus, for example, the cells can be cultured or seeded onto a bio-compatible lattice, such as one that includes extracellular matrix material, synthetic polymers, cytokines, growth factors, etc. Such a lattice can be molded into desired shapes for facilitating the development of tissue types. Also, at least at an early stage during such culturing, the medium and/or substrate is supplemented with factors (e.g., growth factors, cytokines, extracellular matrix material, etc.) that facilitate the development of appropriate tissue types and structures. Indeed, in some embodiments, it is desired to co-culture the cells with mature cells of the respective tissue type, or precursors thereof, or to expose the cells to the respective conditioned medium, as discussed herein.

To facilitate the use of the inventive lipo-derived cells and populations for producing such animal matter and tissues, the invention provides a composition including the inventive cells (and populations) and biologically compatible lattice. Typically, the lattice is formed from polymeric material, having fibers as a mesh or sponge, typically with spaces on the order of between about 100 μm and about 300 μm. Such a structure provides sufficient area on which the cells can grow and proliferate. Desirably, the lattice is biodegradable over time, so that it will be absorbed into the animal matter as it develops. Suitable polymeric lattices, thus, can be formed from monomers such as glycolic acid, lactic acid, propyl fumarate, caprolactone, hyaluronan, hyaluronic acid, and the like. Other lattices can include proteins, polysaccharides, polyhydroxy acids, polyorthoesthers, polyanhydrides, polyphosphazenes, or synthetic polymers (particularly biodegradable polymers). Of course, a suitable polymer for forming such lattice can include more than one monomers (e.g., combinations of the indicated monomers). Also, the lattice can also include hormones, such as growth factors, cytokines, and morphogens (e.g., retinoic acid, arachidonic acid, etc.), desired extracellular matrix molecules (e.g., fibronectin, laminin, collagen, etc.), or other materials (e.g., DNA, viruses, other cell types, etc.) as desired.

To form the composition, the cells are introduced into the lattice such that they permeate into the interstitial spaces therein. For example, the matrix can be soaked in a solution or suspension containing the cells, or they can be infused or injected into the matrix. A particularly preferred composition is a hydrogel formed by crosslinking of a suspension including the polymer and also having the inventive cells dispersed therein. This method of formation permits the cells to be dispersed throughout the lattice, facilitating more even permeation of the lattice with the cells. Of course, the composition also can include mature cells of a desired phenotype or precursors thereof, particularly to potentiate the induction of the inventive stem cells to differentiate appropriately within the lattice (e.g., as an effect of co-culturing such cells within the lattice).

The composition can be employed in any suitable manner to facilitate the growth and generation of the desired tissue

types, structures, or anlagen. For example, the composition can be constructed using three-dimensional or stereotactic modeling techniques. Thus, for example, a layer or domain within the composition can be populated by cells primed for osteogenic differentiation, and another layer or domain within the composition can be populated with cells primed for myogenic and/or chondrogenic development. Bringing such domains into juxtaposition with each other facilitates the molding and differentiation of complex structures including multiple tissue types (e.g., bone surrounded by muscle, such as found in a limb). To direct the growth and differentiation of the desired structure, the composition can be cultured ex vivo in a bioreactor or incubator, as appropriate. In other embodiments, the structure is implanted within the host animal directly at the site in which it is desired to grow the tissue or structure. In still another embodiment, the composition can be engrafted on a host (typically an animal such as a pig, baboon, etc.), where it will grow and mature until ready for use. Thereafter, the mature structure (or anlage) is excised from the host and implanted into the host, as appropriate.

Lattices suitable for inclusion into the composition can be derived from any suitable source (e.g., matrigel), and some commercial sources for suitable lattices exist (e.g., suitable of polyglycolic acid can be obtained from sources such as Ethicon, N.J.). Another suitable lattice can be derived from the acellular portion of adipose tissue—i.e., adipose tissue extracellular matrix matter substantially devoid of cells, and the invention provides such a lipo-derived lattice. Typically, such lipo-derived lattice includes proteins such as proteoglycans, glycoproteins, hyaluronins, fibronectins, collagens (type I, type II, type III, type IV, type V, type VI, etc.), and the like, which serve as excellent substrates for cell growth. Additionally, such lipo-derived lattices can include hormones, preferably cytokines and growth factors, for facilitating the growth of cells seeded into the matrix.

The lipo-derived matrix can be isolated form adipose tissue similarly as described above, except that it will be present in the acellular fraction. For example, adipose tissue or derivatives thereof (e.g., a fraction of the cells following the centrifugation as discussed above) can be subjected to sonic or thermal energy and/or enzymatic processed to recover the matrix material. Also, desirably the cellular fraction of the adipose tissue is disrupted, for example by treating it with lipases, detergents, proteases, and/or by mechanical or sonic disruption (e.g., using a homogenizer or sonicator). However isolated, the material is initially identified as a viscous material, but it can be subsequently treated, as desired, depending on the desired end use. For example, the raw matrix material can be treated (e.g., dialyzed or treated with proteases or acids, etc.) to produce a desirable lattice material. Thus the lattice can be prepared in a hyrated form or it can be dried or lyophilized into a substantially anhydrous form or a powder. Thereafter, the powder can be rehydrated for use as a cell culture substrate, for example by suspending it in a suitable cell culture medium. In this regard, the lipo-derived lattice can be mixed with other suitable lattice materials, such as described above. Of course, the invention pertains to compositions including the lipo-derived lattice and cells or populations of cells, such as the inventive lipo-derived cells and other cells as well (particularly other types of stem cells).

As discussed above, the cells, populations, lattices, and compositions of the invention can be used in tissue engineering and regeneration. Thus, the invention pertains to an implantable structure (i.e., an implant) incorporating any of these inventive features. The exact nature of the implant will vary according to the use to which it is to be put. The implant can be or comprise, as described, mature tissue, or it can include immature tissue or the lattice. Thus, for example, one type of implant can be a bone implant, comprising a population of the inventive cells that are undergoing (or are primed for) osteogenic differentiation, optionally seeded within a lattice of a suitable size and dimension, as described above. Such an implant can be injected or engrafted within a host to encourage the generation or regeneration of mature bone tissue within the patient. Similar implants can be used to encourage the growth or regeneration of muscle, fat, cartilage, tendons, etc., within patients. Other types of implants are anlagen (such as described herein), e.g., limb buds, digit buds, developing kidneys, etc, that, once engrafted onto a patient, will mature into the appropriate structures.

The lipo-derived lattice can conveniently be employed as part of a cell culture kit. Accordingly, the invention provides a kit including the inventive lipo-derived lattice and one or more other components, such as hydrating agents (e.g., water, physiologically-compatible saline solutions, prepared cell culture media, serum or derivatives thereof etc.), cell culture substrates (e.g., culture dishes, plates, vials, etc.), cell culture media (whether in liquid or powdered form), antibiotic compounds, hormones, and the like. While the kit can include any such ingredients, preferably it includes all ingredients necessary to support the culture and growth of desired cell types upon proper combination. Of course, if desired, the kit also can include cells (typically frozen), which can be seeded into the lattice as described herein.

While many aspects of the invention pertain to tissue growth and differentiation, the invention has other applications as well. For example, the lipo-derived lattice can be used as an experimental reagent, such as in developing improved lattices and substrates for tissue growth and differentiation. The lipo-derived lattice also can be employed cosmetically, for example, to hide wrinkles, scars, cutaneous depressions, etc., or for tissue augmentation. For such applications, preferably the lattice is stylized and packaged in unit dosage form. If desired, it can be admixed with carriers (e.g., solvents such as glycerine or alcohols), perfumes, antibiotics, colorants, and other ingredients commonly employed in cosmetic products. The substrate also can be employed autologously or as an allograft, and it can used as, or included within, ointments or dressings for facilitating wound healing. The lipo-dived cells can also be used as experimental reagents. For example, they can be employed to help discover agents responsible for early events in differentiation. For example, the inventive cells can be exposed to a medium for inducing a particular line of differentiation and then assayed for differential expression of genes (e.g., by random-primed PCR or electrophoresis or protein or RNA, etc.).

As any of the steps for isolating the inventive stem cells or the lipo-derived lattice, the, the invention provides a kit for isolating such reagents from adipose tissues. The kit can include a means for isolating adipose tissue from a patient (e.g., a cannula, a needle, an aspirator, etc.), as well as a means for separating stromal cells (e.g., through methods described herein). The kit can be employed, for example, as a bedside source of stem cells that can then be re-introduced from the same individual as appropriate. Thus, the kit can facilitate the isolation of lipo-derived stem cells for implantation in a patient needing regrowth of a desired tissue type, even in the same procedure. In this respect, the kit can also include a medium for differentiating the cells, such as those set forth herein. As appropriate, the cells can be exposed to

the medium to prime them for differentiation within the patient as needed. Of course, the kit can me used as a convenient source of stem cells for in vitro manipulation (e.g., cloning or differentiating as described herein). In another embodiment, the kit can be employed for isolating a lipo-derived lattice as described herein.

EXAMPLES

While one of skill in the art is fully able to practice the instant invention upon reading the foregoing detailed description, the following examples will help elucidate some of its features. In particular, they demonstrate the isolation of a human lipo-derived stem cell substantially free of mature adipocytes, the isolation of a clonal population of such cells, the ability of such cells to differentiate in vivo and in vitro, and the capacity of such cells to support the growth of other types of stem cells. The examples also demonstrate the isolation of a lipo-derived lattice substantially free of cells that is capable of serving as a suitable substrate for cell culture. Of course, as these examples are presented for purely illustrative purposes, they should not be used to construe the scope of the invention in a limited manner, but rather should be seen as expanding upon the foregoing description of the invention as a whole.

The procedures employed in these examples, such as surgery, cell culture, enzymatic digestion, histology, and molecular analysis of proteins and polynucleotides, are familiar to those of ordinary skill in this art. As such, and in the interest of brevity, experimental details are not recited in detail.

Example 1

This example demonstrates the isolation of a human lipo-derived stem cell substantially free of mature adipocytes.

Raw liposuction aspirate was obtained from patients undergoing elective surgery. Prior to the liposuction procedures, the patients were given epinephrine to minimize contamination of the aspirate with blood. The aspirate was strained to separate associated adipose tissue pieces from associated liquid waste. Isolated tissue was rinsed thoroughly with neutral phosphate buffered saline and then enzymatically dissociated with 0.075% w/v colagenase at 37° C. for about 20 minutes under intermittent agitation. Following the digestion, the collagenase was neutralized, and the slurry was centrifuged at about 260 g for about 10 minutes, which produced a multi-layered supernatant and a cellular pellet. The supernatant was removed and retained for further use, and the pellet was resuspended in an erythrocyte-lysing solution and incubated without agitation at about 25° C. for about 10 minutes. Following incubation, the medium was neutralized, and the cells were again centrifuged at about 250 g for about 10 minutes. Following the second centrifugation, the cells were suspended, and assessed for viability (using trypan blue exclusion) and cell number. Thereafter, they were plated at a density of about at about 1×10^6 cells/100 mm dish. They were cultured at 37° C. in DMEM+fetal bovine serum (about 10%) in about 5% CO_2.

The majority of the cells were adherent, small, mononucleic, relatively agranular fibroblast-like cells containing no visible lipid droplets. The majority the cells stained negatively with oil-red O and von Kossa. The cells were also assayed for expression of telomerase (using a commercially available TRAP assay kit), using HeLa cells and HN-12 cells as positive controls. Human foreskin fibroblasts and HN-12 heated cell extracts were used as negative controls. Telomeric products were resolved onto a 12.5% polyacrylamide cells and the signals determined by phosphorimaging. Telemeric ladders representing telomerase activity were observed in the adipose-derived stem cells as well as the positive controls. No ladders were observed in the negative controls.

Thus, these cells were not identifiable as myocytes, adipocytes, chondrocytes, osteocytes, or blood cells. These results demonstrate that the adipose-derived cells express telomerase activity similar to that previously reported for human stem cells.

Subpopulations of these cells were then exposed to the following media to assess their developmental phenotype:

Adipogenesis	Osteogenesis	Myogenesis	Chondrogenesis
DMEM 10% FBS 0.5 mM IBMX 1 μM dexamethasone 10 μM insulin 200 μM indomethacin 1% ABAM	DMEM 10% FBS 5% horse serum 0.1 μM dexamethasone 50 μM ascorbate-2-phosphate 10 mM β-glycerophosphate 1% ABAM	DMEM 10% FBS 5% horse serum 50 μM hydrocortisone 1% ABAM	DMEM 1% FBS 6.25 μg/ml insulin 6.25 μg/ml transferrin 10 ng/ml TGFβ1 50 nM ascorbate-2-phosphate 1% ABAM

A population was cultured at high density in the chondrogenic medium for several weeks. Histological analysis of the tissue culture and paraffin sections was performed with H&E, alcian blue, toludene blue, and Goldner's trichrome staining at 2, 7, and 14 days. Immunohistochemistry was performed using antibodies against chondroitin-4-sulfate and keratin sulfate and type II collagen. Qualitative estimate of matrix staining was also performed. The results indicated that cartilaginous spheroid nodules with a distinct border of perichondral cells formed as early as 48 hours after initial treatment. Untreated control cells exhibited no evidence of chondrogenic differentiation. These results confirm that the stem cells have chondrogenic developmental phenotype.

A population was cultured until near confluence and then exposed to the adipogenic medium for several weeks. The population was examined at two and four weeks after plating by colorimetric assessment of relative opacity following oil red-O staining. Adipogenesis was determined to be underway at two weeks and quite advanced at four weeks (relative opacity of 1 and 5.3, respectively). Bone marrow-derived stem cells were employed as a positive control, and these cells exhibited slightly less adipogenic potential (relative density of 0.7 and 2.8, respectively).

A population was cultured until near confluence and then exposed to the osteogeneic medium for several weeks. The

population was examined at two and four weeks after plating by colorimetric assessment of relative opacity following von Kossa staining. Osteogenesis was determined to be underway at two weeks and quite advanced at four weeks (relative opacity of 1.1 and 7.3, respectively. Bone marrow-derived stem cells were employed as a positive control, and these cells exhibited slightly less osteogenic potential (relative density of 0.2 and 6.6, respectively).

A population was cultured until near confluence and then exposed to the myogenic medium for several weeks. The population was examined at one, three, and six weeks after plating by assessment of multinucleated cells and expressin of muscle-specific proteins (MyoD and myosin heavy chain). Human foreskin fibroblasts and skeletal myoblasts were used as controls. Cells expressing MyoD and myosin were found at all time points following exposure to the myogenic medium in the stem cell population, and the proportion of such cells increased at 3 and 6 weeks. Multinucleated cells were observed at 6 weeks. In contrast, the fibroblasts exhibited none of these characteristics at any time points.

These results demonstrate the isolation of a human lipo-derived pluripotent stem cell substantially free of mature adipocytes.

Example 2

This example demonstrates that lipo-derived stem cells do not differentiate in response to 5-azacytidine.

Lipo-derived stem cells obtained in accordance with Example 1 were cultured in the presence of 5-azacytidine. In contrast with bone marrow-derived stem cells, exposure to this agent did not induce myogenic differentiation (see Wakitani et al., supra).

Example 3

This example demonstrates the generation of a clonal population of human lipo-derived stem cells.

Cells isolated in accordance with the procedure set forth in Example 1 were plated at about 5,000 cells/100 mm dish and cultured for a few days as indicated in Example 1. After some rounds of cell division, some clones were picked with a cloning ring and transferred to wells in a 48 well plate. These cells were cultured for several weeks, changing the medium twice weekly, until they were about 80% to about 90% confluent (at 37° C. in about 5% CO_2 in ⅔ F_{12}medium+ 20% fetal bovine serum and ⅓ standard medium that was first conditioned by the cells isolated in Example 1, "cloning medium"). Thereafter, each culture was transferred to a 35 mm dish and grown, and then retransferred to a 100 mm dish and grown until close to confluent. Following this, one cell population was frozen, and the remaining populations were plated on 12 well plates, at 1000 cells/well.

The cells were cultured for more than 15 passages in cloning medium and monitored for differentiation as indicated in Example 1. The undifferentiated state of each clone remained true after successive rounds of differentiation.

Populations of the clones then were established and exposed to adipogenic, chondrogenic, myogenic, and osteogenic medium as discussed in Example 1. It was observed that at least one of the clones was able to differentiate into bone, fat, cartilage, and muscle when exposed to the respective media, and most of the clones were able to differentiate into at least three types of tissues. The capacity of the cells to develop into muscle and cartilage further demonstrates the pluripotentiality of these lipo-derived stem cells.

These results demonstrate that the lipo-derived stem cells can be maintained in an undifferentiated state for many passages without the requirement for specially pre-screened lots of serum. The results also demonstrate that the cells retain pluripotentiality following such extensive passaging, proving that the cells are indeed stem cells and not merely committed progenitor cells.

Example 4

This example demonstrates the lipo-derived stem cells can support the culture of other types of stem cells.

Human lipo-derived stem cells were passaged onto 96 well plates at a density of about 30,000/well, cultured for one week and then irradiated. Human CD34+ hematopoetic stem cells isolated from umbilical cord blood were then seeded into the wells. Co-cultures were maintained in MyelocCult H5100 media, and cell viability and proliferation were monitored subjectively by microscopic observation. After two weeks of co-culture, the hematopoetic stem cells were evaluated for CD34 expression by flow cytometry.

Over a two-week period of co-culture with stromal cells, the hematopoetic stem cells formed large colonies of rounded cells. Flow analysis revealed that 62% of the cells remained CD34+. Based on microscopic observations, human adipo-derived stromal cells maintained the survival and supported the growth of human hematopoetic stem cells derived from umbilical cord blood.

These results demonstrate that stromal cells from human subcutaneous adipose tissue are able to support the ex vivo maintenance, growth and differentiation of other stem cells.

Example 5

This example demonstrates that the lipo-derived stem cells can differentiate in vivo.

Four groups (A–D) of 12 athymic mice each were implanted subcutaneously with hydroxyapatite/tricalcium phosphate cubes containing the following: Group A contained lipo-derived stem cells that had been pretreated with osteogenic medium as set forth in Example 1. Group B contained untreated lipo-derived stem cells. Group C contained osteogenic medium but no cells. Group D contained non-osteogenic medium and no cells. Within each group, six mice were sacrificed at three weeks, and the remaining mice sacrificed at eight weeks following implantation. The cubes were extracted, fixed, decalcified, and sectioned. Each section was analyzed by staining with H&E, Mallory bone stain, and immunostaining for osteocalcin.

Distinct regions of osteoid-like tissue staining for osteocalcin and Mallory bone staining was observed in sections from groups A and B. Substantially more osteoid tissue was observed in groups A and B than in the other groups ($p<0.05$ ANOVA), but no significant difference in osteogenesis was observed between groups A and B. Moreover, a qualitative increase in bone growth was noted in both groups A and B between 3 and 8 weeks. These results demonstrate that the lipo-derived stem cells can differentiate in vitro.

Example 6

This example demonsrates the isolation of a lipo-derived lattice substantially devoid of cells.

In one protocol withheld supernatant from Example 1 was subjected to enzymatic digestion for three days in 0.05% trypsin EDTA/100 U/ml deoxyribonuclease to destroy the cells. Every day the debris was rinsed in saline and fresh enzyme was added. Thereafter the material was rinsed in

saline and resuspended in 0.05% collagease and about 0.1% lipase to partially digest the proteins and fat present. This incubation continued for two days.

In another protocol, the withheld supernatant from Example 1 was incubated in EDTA to eliminate any epithelial cells. The remaining cells were lysed using a buffer containing 1% NP40, 0.5% sodium deoxycholate, 0.1% SDS, 5 mM EDTA, 0.4M NaCl, 50 mMTris-HCL (pH8) and protease inhibitors, and 10 μg/ml each of leupeptin, chymostatin, antipain, and pepstatin A. Finally, the tissue was extensively washed in PBS without divalent cations.

After both preparatory protocols, remaining substance was washed and identified as a gelatinous mass. Microscopic analysis of this material revealed that it contained no cells, and it was composed of high amounts of collagen (likely type IV) and a wide variety of growth factors. Preparations of this material have supported the growth of cells, demonstrating it to be an excellent substrate for tissue culture.

Incorporation by Reference

All sources (e.g., inventor's certificates, patent applications, patents, printed publications, repository accessions or records, utility models, world-wide web pages, and the like) referred to or cited anywhere in this document or in any drawing, Sequence Listing, or Statement filed concurrently herewith are hereby incorporated into and made part of this specification by such reference thereto.

Guide to Interpretation

The foregoing is an integrated description of the invention as a whole, not merely of any particular element of facet thereof. The description describes "preferred embodiments" of this invention, including the best mode known to the inventors for carrying it out. Of course, upon reading the foregoing description, variations of those preferred embodiments will become obvious to those of ordinary skill in the art The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law.

As used in the foregoing description and in the following claims, singular indicators (eg., "a" or "one") include the plural, unless otherwise indicated. Recitation of a range of discontinuous values is intended to serve as a shorthand method of referring individually to each separate value falling within the range, and each separate value is incorporated into the specification as if it were individually listed Additionally, the following terms are defined as follows:

An anlage is a primordial structure that has a capacity to develop into a specific mature structure.

A developmental phenotype is the potential of a cell to acquire a particular physical phenotype through the process of differentiation.

A hormone is any substance that is secreted by a cell and that causes a phenotypic change in the same or another cell upon contact.

A stem cell is a pluripotent cell that has the capacity to differentiate in accordance with at least two discrete developmental pathways.

As regards the claims in particular, the term "consisting essentially of" indicates that unlisted ingredients or steps that do not materially affect the basic and novel properties of the invention can be employed in addition to the specifically recited ingredients or steps. In contrast, terms such as "comprising," "having," and "including" indicate that any ingredients or steps can be present in addition to those recited. The term "consisting of" indicates that only the recited ingredients or steps are present, but does not foreclose the possibility that equivalents of the ingredients or steps can substitute for those specifically recited.

We claim:

1. An isolated adipose-derived stem cell that can differentiate into two or more of the group consisting of a bone cell, a cartilage cell, a nerve cell, or a muscle cell.

2. An isolated, adipose-derived multipotent cell that differentiates into cells of two or more mesodermal phenotypes.

3. An isolated adipose-derived stem cell that differentiates into two or more of the group consisting of a fat cell, a bone cell, a cartilage cell, a nerve cell, or a muscle cell.

4. An isolated adipose-derived stem cell that differentiates into a combination of any of a fat cell, a bone cell, a cartilage cell, a nerve cell, or a muscle cell.

5. A substantially homogeneous population of adipose-derived stem cells, comprising a plurality of the stem cell of claim 1, 3 or 4.

6. The adipose-derived stem cell of claim 1, 3 or 4 which can be cultured for at least 15 passages without differentiating.

7. The adipose-derived stem cell of claim 1, 3 or 4 which is human.

8. The cell of any of claim 1, 3 or 4 which is genetically modified.

9. The cell of any of claim 1, 3 or 4, which has a cell-surface bound intercellular signaling moiety.

10. The cell of any of claim 1, 3 or 4, which secretes a hormone.

* * * * *

B

AO88 (Rev. 1/94) Subpoena in a Civil Case

Issued from the

UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

UNIVERSITY OF PITTSBURGH of the Commonwealth System of Higher Education,

Plaintiff,

v.

Marc H. HEDRICK et al.

Defendants.

SUBPOENA IN A CIVIL CASE

Case Number: C.A. No. 2:04-09014 Litigation pending in U.S. District Court, Central District of California (Western District – Los Angeles)

TO: **Olympus Corporation**
Olympus America Inc.
2 Corporate Center Drive
Melville, NY 11747-3157

☐ YOU ARE COMMANDED to appear in the United States District Court at the place, date, and time specified below to testify in the above case

PLACE OF TESTIMONY	COURTROOM
	DATE AND TIME

☒ YOU ARE COMMANDED to appear at the place, date, and time specified below to testify at the taking of a deposition in the above case. See schedule A attached.

PLACE OF DEPOSITION	DATE AND TIME
DRINKER, BIDDLE & REATH LLP 140 Broadway, 39th Floor, New York, NY 10005-1116	Tuesday February 27, 2006 9:00 A.M.

☐ YOU ARE COMMANDED to produce and/or permit inspection and copying of the following documents or objects at the place, date, and time specified below (list documents or objects): See schedule A attached.

PLACE	DATE AND TIME

☐ YOU ARE COMMANDED to permit inspection of the following premises at the date and time specified below:

PREMISES	DATE

Any organization not a party to this suit that is subpoenaed for the taking of a deposition shall designate one or more officers, directors, or managing agents, or other persons who consent to testify on its behalf, and may set forth, for each person designated, the matters on which the person will testify. Federal Rules of Civil Procedure, 30(b)(6).

ISSUING OFFICER SIGNATURE AND TITLE (INDICATE IF ATTORNEY FOR PLAINTIFF OR DEFENDANT)	DATE
Attorney for Plaintiff	February 9, 2006

ISSUING OFFICERS' NAME, ADDRESS AND PHONE NUMBER
Kathryn R. Doyle, Drinker Biddle & Reath LLP, One Logan Square, 18th and Cherry Streets, Philadelphia, PA 19103-6996
215-988-2902

(See Rule 45, Federal Rules of Civil Procedure, Parts C & D on Reverse)

Rule 45 of the Federal Rules of Civil Procedure grants you the following Protections:

(c) Protection of Persons Subject to Subpoenas.

(1) A party or an attorney responsible for the issuance and service of a subpoena shall take reasonable steps to avoid imposing undue burden or expense on a person subject to that subpoena. The court on behalf of which the subpoena was issued shall enforce this duty and impose upon the party or attorney in breach of this duty an appropriate sanction, which may include, but is not limited to, lost earnings and a reasonable attorney's fee.

(2) (A) A person commanded to produce and permit inspection and copying of designated books, papers, documents or tangible things, or inspection of premises need not appear in person at the place of production or inspection unless commanded to appear for deposition, hearing or trial.

(B) Subject to paragraph (d)(2) of this rule, a person commanded to produce and permit inspection and copying may, within 14 days after service of the subpoena or before the time specified for compliance if such time is less than 14 days after service, serve upon the party or attorney designated in the subpoena written objection to inspection or copying of any or all of the designated materials or of the premises. If objection is made, the party serving the subpoena shall not be entitled to inspect and copy the materials or inspect the premises except pursuant to an order of the court by which the subpoena was issued. If objection has been made, the party serving the subpoena may, upon notice to the person commanded to produce, move at any time for an order to compel the production. Such an order to compel production shall protect any person who is not a party or an officer of a party from significant expense resulting from the inspection and copying commanded.

(3) (A) On timely motion, the court by which a subpoena was issued shall quash or modify the subpoena if it

(i) fails to allow reasonable time for compliance;

(ii) requires a person who is not a party or an officer of a party to travel to a place more than 100 miles from the place where that person resides, is employed or regularly transacts business in person, except that, subject to the provisions of clause (c)(3)(B)(iii) of this rule, such a person may in order to attend trial be commanded to travel from any such place within the state in which the trial is held, or

(iii) requires disclosure of privileged or other protected matter and no exception or waiver applies, or

(iv) subjects a person to undue burden.

(B) If a subpoena

(i) requires disclosure of a trade secret or other confidential research, development, or commercial information, or

(ii) requires disclosure of an unretained expert's opinion or information not describing specific events or occurrences in dispute and resulting from the expert's study made not at the request of any party, or

(iii) requires a person who is not a party or an officer of a party to incur substantial expense to travel more than 100 miles to attend trial,

the court may, to protect a person subject to or affected by the subpoena, quash or modify the subpoena or, if the party in whose behalf the subpoena is issued shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship and assures that the person to whom the subpoena is addressed will be reasonably compensated, the court may order appearance or production only upon specified conditions.

SCHEDULE A:

The deposition will encompass the following topics for the designated witness(es):

1. All communications with Cytori Therapeutics, Inc. ("Cytori") that reference U.S. Pat. 6,777,231 in any way.

2. All communications with Cytori that reference the civil action *University of Pittsburgh et al v. Hedrick et al.*, 04-cv-09014 (Central District of California).

3. All communications between Dr. Marc Hedrick and Olympus Corporation.

4. All communications with Cytori that reference an inventorship dispute about U.S. Pat. 6,777,231.

5. All communications with investment brokers, managers, bankers, or financial company representatives of any type regarding U.S. Pat. 6,777,231, its technology, its inventorship, Dr. Marc Hedrick, Cytori, an inventorship dispute about U.S. Pat. 6,777,231, or the civil action *University of Pittsburgh et al v. Hedrick et al.*, 04-cv-09014 (Central District of California).

6. All communications with equity investors, analysts, securities dealers, or NASDAQ representatives regarding U.S. Pat. 6,777,231, its technology, Cytori, an inventorship dispute about U.S. Pat. 6,777,231, Dr. Marc Hedrick, or the civil action *University of Pittsburgh et al v. Hedrick et al.*, 04-cv-09014 (Central District of California).

7. All references in the joint venture documents and dealings between Cytori and Olympus Corporation to U.S. Pat. 6,777,231, its technology, an inventorship dispute about U.S. Pat. 6,777,231, Dr. Marc Hedrick, or the civil action *University of Pittsburgh et al v. Hedrick et al.*, 04-cv-09014 (Central District of California).

8. The collaboration between Cytori and Olympus Corporation.

AO88 (Rev. 1/94) Subpoena in a Civil Case

Issued from the

UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF NEW YORK

UNIVERSITY OF PITTSBURGH of the Commonwealth System of Higher Education,

Plaintiff,

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Defendants.

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PLACE OF DEPOSITION	DATE AND TIME

☒ YOU ARE COMMANDED to produce and/or permit inspection and copying of the following documents or objects at the place, date, and time specified below (list documents or objects): See schedule B attached.

PLACE	DATE AND TIME
DRINKER, BIDDLE & REATH LLP 140 Broadway, 39th Floor New York, NY 10005-1116	February 22, 2006 10:00 A.M.

☐ YOU ARE COMMANDED to permit inspection of the following premises at the date and time specified below:

PREMISES	DATE

Any organization not a party to this suit that is subpoenaed for the taking of a deposition shall designate one or more officers, directors, or managing agents, or other persons who consent to testify on its behalf, and may set forth, for each person designated, the matters on which the person will testify. Federal Rules of Civil Procedure, 30(b)(6).

ISSUING OFFICER SIGNATURE AND TITLE (INDICATE IF ATTORNEY FOR PLAINTIFF OR DEFENDANT)	DATE
Attorney for plaintiff	February 9, 2006

ISSUING OFFICER'S NAME, ADDRESS AND PHONE NUMBER
Kathryn R. Doyle, Drinker Biddle & Reath LLP, One Logan Square, 18th and Cherry Streets, Philadelphia, PA 19103-6996
215-988-2902

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(2) (A) A person commanded to produce and permit inspection and copying of designated books, papers, documents or tangible things, or inspection of premises need not appear in person at the place of production or inspection unless commanded to appear for deposition, hearing or trial.

(B) Subject to paragraph (d)(2) of this rule, a person commanded to produce and permit inspection and copying may, within 14 days after service of the subpoena or before the time specified for compliance if such time is less than 14 days after service, serve upon the party or attorney designated in the subpoena written objection to inspection or copying of any or all of the designated materials or of the premises. If objection is made, the party serving the subpoena shall not be entitled to inspect and copy the materials or inspect the premises except pursuant to an order of the court by which the subpoena was issued. If objection has been made, the party serving the subpoena may, upon notice to the person commanded to produce, move at any time for an order to compel the production. Such an order to compel production shall protect any person who is not a party or an officer of a party from significant expense resulting from the inspection and copying commanded.

(3) (A) On timely motion, the court by which a subpoena was issued shall quash or modify the subpoena if it

(i) fails to allow reasonable time for compliance;

(ii) requires a person who is not a party or an officer of a party to travel to a place more than 100 miles from the place where that person resides, is employed or regularly transacts business in person, except that, subject to the provisions of clause (c)(3)(B)(iii) of this rule, such a person may in order to attend trial be commanded to travel from any such place within the state in which the trial is held, or

(iii) requires disclosure of privileged or other protected matter and no exception or waiver applies, or

(iv) subjects a person to undue burden.

(B) If a subpoena

(i) requires disclosure of a trade secret or other confidential research, development, or commercial information, or

(ii) requires disclosure of an unretained expert's opinion or information not describing specific events or occurrences in dispute and resulting from the expert's study made not at the request of any party, or

(iii) requires a person who is not a party or an officer of a party to incur substantial expense to travel more than 100 miles to attend trial,

the court may, to protect a person subject to or affected by the subpoena, quash or modify the subpoena or, if the party in whose behalf the subpoena is issued shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship and assures that the person to whom the subpoena is addressed will be reasonably compensated, the court may order appearance or production only upon specified conditions.

INSTRUCTIONS:

Definitions:

A. "Document" includes "things' and is used in its customary broad sense under the Federal Rules of Civil Procedure and includes every writing or record of every type and description.

B. "Communication" is used in its customary broad sense under the Federal Rules of Civil Procedure and means and includes any transmission or exchange of information between two or more persons, whether orally or in writing, including without limitation any conversation or discussion by means of letter, note, memorandum, inter-office correspondence, telephone, telegraph, telex, telecopies, cable communicating data processors, e-mail, or some other electronic or other medium.

C. The term "and/or" shall be construed in both the conjunctive and disjunctive and shall serve as a request for all information that would be responsive under a conjunctive reading in addition to all information that would be responsive under a disjunctive reading.

D. The term "relating to" shall mean having any connection, relation, or reference to and include, by way of example and without limitation, discussing, identifying, containing, showing, evidencing, describing, reflecting, dealing with, regarding, pertaining to, analyzing, evaluating, estimating, constituting, comprising, studying, surveying, projecting, recording, summarizing, assessing, criticizing, reporting, commenting on, referring to in any way, either directly or indirectly, or otherwise involving, in whole or in part. Documents and communications "relating to" or that "relate(s) to" the subject matter specified in a Document Request includes without limitation documents and communications underlying or supporting, or utilized in the preparation of, any documents or communications responsive to each Document Request.

E. The singular includes plural, and vice versa. The masculine includes feminine and neuter genders. The past tense includes the present tense where the clear meaning is not distorted by change of tense.

F. To the extent that any documents will be withheld under a claim of an applicable privilege, provide a description of each such document withheld that includes a description of the nature of the document withheld, the date the document was generated, all recipients of the document, the privilege asserted and the general subject matter of the document.

SCHEDULE A:

Please produce the following documents:

1. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting communications with Cytori Therapeutics, Inc. ("Cytori") that reference U.S. Pat. 6,777,231 in any way.

2. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting communications with Cytori that reference the civil action *University of Pittsburgh et al v. Hedrick et al.*, 04-cv-09014 (Central District of California).

3. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting communications between Dr. Marc Hedrick and Olympus Corporation.

4. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting communications with Cytori that reference an inventorship dispute about U.S. Pat. 6,777,231.

5. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting any communications with investment brokers, managers, bankers, or financial company representatives of any type regarding U.S. Pat. 6,777,231, its technology, its inventorship, Dr. Marc Hedrick, Cytori, an inventorship dispute about U.S. Pat. 6,777,231, or the civil action *University of Pittsburgh et al v. Hedrick et al.*, 04-cv-09014 (Central District of California).

6. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting any communications with equity investors, analysts, securities dealers, or NASDAQ representatives regarding U.S. Pat. 6,777,231, its technology, Cytori, an inventorship dispute

about U.S. Pat. 6,777,231, Dr. Marc Hedrick, or the civil action *University of Pittsburgh et al v. Hedrick et al.*, 04-cv-09014 (Central District of California).

7. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting any references in the joint venture documents between Olympus Corporation and Cytori to U.S. Pat. 6,777,231, its technology, an inventorship dispute about U.S. Pat. 6,777,231, Dr. Marc Hedrick, or the civil action *University of Pittsburgh et al v. Hedrick et al.*, 04-cv-09014 (Central District of California).

NYS Department of State

Division of Corporations

Entity Information

Selected Entity Name: OLYMPUS CORPORATION

Selected Entity Status Information

Current Entity Name: OLYMPUS CORPORATION
Initial DOS Filing Date: JANUARY 18, 1990
County: SUFFOLK
Jurisdiction: NEW YORK
Entity Type: DOMESTIC BUSINESS CORPORATION
Current Entity Status: ACTIVE

Selected Entity Address Information

DOS Process (Address to which DOS will mail process if accepted on behalf of the entity)
C/O OLYMPUS AMERICA INC
ATT TAX DEPT
2 CORPORATE CENTER DR
MELVILLE, NEW YORK, 11747-3157

Chairman or Chief Executive Officer
MASAHARU OKUBO
TWO CORPORATE CENTER DRIVE
MELVILLE, NEW YORK, 11747

Principal Executive Office
OLYMPUS CORPORATION
TWO CORPORATE CENTER DRIVE
MELVILLE, NEW YORK, 11747

Registered Agent
NONE

NOTE: New York State does not issue organizational identification numbers.

Search Results New Search

Division of Corporations, State Records and UCC Home Page NYS Department of State Home Page

D

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Attorneys for
OLYMPUS CORPORATION

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

UNIVERSITY OF PITTSBURGH OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION, Plaintiff, v. MARC H. HEDRICK et al. Defendants.	**OBJECTIONS TO DEPOSITION SUBPOENA IN A CIVIL CASE DIRECTED TO OLYMPUS CORPORATION** (Litigation pending in U.S. District Court, Central District of California – Case No. CV-04-9014 CBM (AJWx))

COMES NOW OLYMPUS CORPORATION, and specially appears solely to object to the deposition subpoena that has been served upon Olympus America Inc., arising from litigation to which it is not a party and pending in the U.S. District Court, Central District of California – Case No. CV-04-9014 CBM (AJWx) ("the underlying litigation").

GENERAL OBJECTIONS

1. Olympus Corporation objects to the service of the subpoena which was attempted through another entity, for which service is improper in view of the legal requirements for service of a subpoena on a foreign entity as provided in, for example, Jazini v. Nissan Motor Co., 148 F.3d 181, 184 (2d Cir. 1998).

[redacted]

2. Olympus Corporation objects to the deposition subpoena in that it is directed to matters irrelevant to the issues of the underlying litigation as presently understood by Olympus Corporation.

3. Olympus Corporation objects to the deposition subpoena in that the discovery sought by the subpoena results in an undue and unnecessary burden wherein Olympus Corporation is not a party to the underlying litigation.

4. Olympus Corporation objects to the deposition subpoena in that the discovery sought by the subpoena is directed to matters that are highly confidential to the ongoing business activities of Olympus Corporation and substantial harm would result from the disclosure of such information unnecessarily.

5. Olympus Corporation objects to the deposition subpoena in that it seeks information protected by the attorney client privilege or the work product doctrine or both.

6. Olympus Corporation objects to the deposition subpoena in that it seeks discovery that is the subject of confidentiality agreements with others who are not a party to the underlying litigation.

7. Olympus Corporation objects to the deposition subpoena to the extent that the discovery sought by the subpoena can be more readily and with less burden obtained from a party to the underlying litigation, or from another entity (e.g., Cytori Therapeutics) that has more familiarity with the underlying litigation.

8. Olympus Corporation objects to the time, date and/or location for the deposition. The subpoena seeks that a knowledgeable individual appear for a deposition in New York City, notwithstanding the requirements of Rule 45(c)(3)(A)(ii) that provides that a deposition is not permitted that "requires a person who is not a party or an officer of a party to travel to a place more than 100 miles from the place where that person resides, is employed or regularly transacts business in person." No such person is known to exist.

[redacted]

SPECIFIC OBJECTIONS

1. All communications with Cytori Therapeutics, Inc. ("Cytori") that reference U.S. Pat. 6,777,231 in any way.

Response:

See General Objections, which are incorporated herein by reference.

2. All communications with Cytori that reference the civil action University of Pittsburgh et al v. Hedrick et al., 04-cv-09014 (Central District of California).

Response:

See General Objections, which are incorporated herein by reference.

3. All communications between Dr. Marc Hedrick and Olympus Corporation.

Response:

See General Objections, which are incorporated herein by reference.

4. All communications with Cytori that reference an inventorship dispute about U.S. Pat. 6,777,231.

Response:

See General Objections, which are incorporated herein by reference.

5. All communications with investment brokers, managers, bankers, or financial company representatives of any type regarding U.S. Pat. 6,777,231, its technology, its inventorship, Dr. Marc Hedrick, Cytori, an inventorship dispute about U.S. Pat. 6,777,231, or the civil action University of Pittsburgh et al v. Hedrick et al., 04-cv-09014 (Central District of California).

Response:

In addition to the General Objections, which are incorporated herein by reference, Olympus objects to this request as ambiguous in the use of the word "managers" and in the use of the words "its inventorship" and in the use of the words "its technology."

[redacted]

6. All communications with equity investors, analysts, securities dealers, or NASDAQ representatives regarding U.S. Pat. 6,777,231, its technology, Cytori, an inventorship dispute about U.S. Pat. 6,777,231, Dr. Marc Hedrick, or the civil action University of Pittsburgh et al v. Hedrick et al., 04-cv-09014 (Central District of California).

Response:

In addition to the General Objections, which are incorporated herein by reference, Olympus objects to this request as ambiguous in the use of the words "equity investors" and in the use of the words "its technology."

7. All references in the joint venture documents between Cytori and Olympus Corporation to U.S. Pat. 6,777,231, its technology, an inventorship dispute about U.S. Pat. 6,777,231, Dr. Marc Hedrick, or the civil action University of Pittsburgh et al v. Hedrick et at., 04-cv-09014 (Central District of California).

Response:

In addition to the General Objections, which are incorporated herein by reference, Olympus objects to this request as ambiguous in the use of the words "its technology."

8. The collaboration between Cytori and Olympus Corporation.

Response:

In addition to the General Objections, which are incorporated herein by reference, Olympus objects to this request as ambiguous in the use of the word "collaboration."

Respectfully submitted,

SIDLEY AUSTIN LLP

Dated: February 22, 2006

By: _____
Jeffrey M. Olson
Attorneys for
OLYMPUS CORPORATION

[redacted]

CERTIFICATE OF SERVICE

I hereby certify that on February 22, 2006, I caused true and correct copies of the foregoing **OBJECTIONS TO DEPOSITION SUBPOENA IN A CIVIL CASE DIRECTED TO OLYMPUS CORPORATION** to be served by PDF and first class mail delivery to:

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Attorneys for
OLYMPUS CORPORATION

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

UNIVERSITY OF PITTSBURGH OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION, Plaintiff, v. MARC H. HEDRICK et al., Defendants.	**OBJECTIONS TO SUBPOENA DUCES TECUM IN A CIVIL CASE DIRECTED TO OLYMPUS CORPORATION** (Litigation pending in U.S. District Court, Central District of California – Case No. CV-04-9014 CBM (AJWx))

COMES NOW OLYMPUS CORPORATION, and specially appears solely to object to the subpoena duces tecum that has been served upon Olympus America Inc., arising from litigation to which it is not a party and pending in the U.S. District Court, Central District of California – Case No. CV-04-9014 CBM (AJWx) ("the underlying litigation").

GENERAL OBJECTIONS

1. Olympus Corporation objects to the service of the subpoena which was attempted through another entity, for which service is improper in view of the legal requirements for service of a subpoena on a foreign entity as provided in, for example, Jazini v. Nissan Motor Co., 148 F.3d 181, 184 (2d Cir. 1998).

[redacted]

2. Olympus Corporation objects to each and every document request as the discovery sought by the subpoena is directed to matters irrelevant to the issues of the underlying litigation as presently understood by Olympus Corporation.

3. Olympus Corporation objects to each and every document request as the discovery sought by the subpoena results in an undue and unnecessary burden wherein Olympus Corporation is not a party to the underlying litigation.

4. Olympus Corporation objects to each and every document request as the discovery sought by the subpoena is directed to matters that are highly confidential to the ongoing business activities of Olympus Corporation and substantial harm would result from the disclosure of these documents unnecessarily.

5. Olympus Corporation objects to each and every document request to the extent it seeks information protected by the attorney client privilege or the work product doctrine or both.

6. Olympus Corporation objects to each and every document request to the extent that the discovery sought by the subpoena is the subject of confidentiality agreements with others who are not a party to the underlying litigation.

7. Olympus Corporation objects to each and every document request to the extent that the discovery sought by the subpoena can be more readily and with less burden obtained from a party to the underlying litigation, or from another entity (e.g., Cytori Therapeutics) that has more familiarity with the underlying litigation.

8. Olympus Corporation objects to the time, date and/or location for the production of the documents.

SPECIFIC OBJECTIONS

1. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting communications with Cytori Therapeutics, Inc. ("Cytori") that reference U.S. Pat. 6,777,231 in any way.

Response:

In addition to the General Objections, which are incorporated herein by reference, Olympus objects to this request as ambiguous in the use of the words "reflecting communications."

[redacted]

2. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting communications with Cytori that reference the civil action University of Pittsburgh et al v. Hedrick et at., 04-cv-09014 (Central District of California).

Response:

In addition to the General Objections, which are incorporated herein by reference, Olympus objects to this request as ambiquous in the use of the words "reflecting communications."

3. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting communications between Dr. Marc Hedrick and Olympus Corporation.

Response:

In addition to the General Objections, which are incorporated herein by reference, Olympus objects to this request as ambiquous in the use of the words "reflecting communications."

4. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting communications with Cytori that reference an inventorship dispute about U.S. Pat. 6,777,231.

Response:

In addition to the General Objections, which are incorporated herein by reference, Olympus objects to this request as ambiquous in the use of the words "reflecting communications."

5. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting any communications with investment brokers, managers, bankers, or financial company representatives of any type regarding U.S. Pat. 6,777,231, its technology, its inventorship, Dr. Marc Hedrick, Cytori, an inventorship dispute about U. S. Pat. 6,777,231, or the civil action University of Pittsburgh et al v. Hedrick et at., 04-cv-09014 (Central District of California).

[redacted]

Response:

In addition to the General Objections, which are incorporated herein by reference, Olympus objects to this request as ambiguous in the use of the words "reflecting any communications" and in the use of the word "managers" and in the use of the words "its inventorship" and in the use of the words "its technology."

6. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting any communications with equity investors, analysts, securities dealers, or NASDAQ representatives regarding U.S. Pat. 6,777,231, its technology, Cytori, an inventorship dispute about U.S. Pat. 6,777,231, Dr. Marc Hedrick, or the civil action University of Pittsburgh et al v. Hedrick et at., 04-cv-09014 (Central District of California).

Response:

In addition to the General Objections, which are incorporated herein by reference, Olympus objects to this request as ambiguous in the use of the words "reflecting any communications" and in the use of the words "equity investors" and in the use of the words "its technology."

7. All correspondence, memoranda, e-mails, notes and other documents in any manner reflecting any references in the joint venture documents between Olympus Corporation and Cytori to U.S. Pat. 6,777,231, its technology, an inventorship dispute about U.S. Pat. 6,777,231, Dr. Marc Hedrick, or the civil action University of Pittsburgh et al v. Hedrick et al., 04-cv-09014 (Central District of California).

[redacted]

Response:

In addition to the General Objections, which are incorporated herein by reference, Olympus objects to this request as ambiquous in the use of the words "reflecting any references" and in the use of the words "its technology."

Respectfully submitted,

SIDLEY AUSTIN LLP

Dated: February 22, 2006

By: _____
Jeffrey M. Olson
Attorneys for
OLYMPUS CORPORATION

[redacted]

CERTIFICATE OF SERVICE

I hereby certify that on February 22, 2006, I caused true and correct copies of the foregoing **OBJECTIONS TO SUBPOENA DUCES TECUM IN A CIVIL CASE DIRECTED TO OLYMPUS CORPORATION** to be served by PDF and first class mail delivery to:

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March 14, 2006

Via E-Mail and First Class Mail

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RE: Confirmation of 3/13 Conference Call Discussions
***University of Pittsburgh v. Hedrick*, 04-9014-CBM (AJWx)**

Dear Counsel:

I write to memorialize our discussion that we had on the telephone this afternoon. Jay DelMaster, John Marshall, George Awad, David Kessler and I were on the call for plaintiff and the three of you were on the phone for defendants and several third-parties.

University of Pittsburgh Discovery Requests

We agreed to conduct Mark Hedrick's deposition on Thursday, March 23 and Cytori Therapeutics Inc.'s ("Cytori") / Christopher J. Calhoun's deposition/ on Friday, March 24 in San Diego. You have agreed to produce documents for Marc Hedrick (to the extent any exist) and Cytori in the next few days. While you did not have an opportunity to review our subpoena of Mr. Calhoun before the conference call, on our representation that the subpoena's scope was substantially similar to the Cytori subpoena, you believed that you would be able to produce any of his documents in advance of his deposition on March 24.

You represented that you did not plan on producing any documents from Olympus and that you recommended that we review the documents produced by Cytori before pushing further for Olympus documents. We agreed to wait and review Cytori's documents to see if we needed additional documents from Olympus before seeking assistance from the court based on your representation that we would have the Cytori documents in the next few days. If we believe that we need additional documents after reviewing the Cytori documents, we will let you know as soon as reasonably possible.

Established 1849

PHLIT\555275\1

[redacted]

Based upon your representation that the Cytori/Olympus Joint Venture (JV) has no employees and possesses and/or controls no documents that are not in the possession and/or control of Cytori, we agreed there was no reason to conduct a deposition or obtain documents of the JV. Thus, we will hold the subpoena in abeyance unless its is discovered that the JV possess unique documents or information.

You agreed that UC will produce documents in the next ten days, by March 23, and that the deposition of UC's designee, Mr. Shih, will hopefully be in San Francisco on March 27. Can you confirm his availability by tomorrow?

We broached the issue of Hedrick paying our expenses for his agreed-upon deposition for which he failed to appear. You explained that we would need to get a Court order to obtain that money.

Defendants Discovery Requests

All of the CellSource materials that we agreed we would produce – the pleadings and the deposition transcripts of John Johnson and Alan Garfinkel – have been produced to Defendants.

Pursuant to your second 30(b)(6) Deposition Notice, we agreed to produce Fran Connell on March 30 and another designee to respond to non-objectionable portions of your Deposition Notice on March 31, both in our offices in Philadelphia. We will serve you with formal objections to your new 30(b)(6) Notice by tomorrow.

With respect to your letter dated March 10, you requested clarification regarding U. Pitt's responses to your Second Set of Document Requests and Interrogatories. With respect to the document request responses, U. Pitt. does not expect to produce any additional documents in the face of your requests except: (1) we are still attempting to attempt to obtain relevant and responsive notebooks from Dr. Llull; and (2) we are completing our search for electronic documents in the possession or control of U. Pitt. We hope to have an answer to both of these inquiries by the end of Thursday and, to the extent relevant, responsive, non-objectionable, non-privileged documents are found, they will be produced to you as soon as reasonably possible thereafter. Of course, if unexpected additional documents surface that are relevant, responsive, non-objectionable and not privileged, we are obligated (just as you are) to supplement our production and will do so.

[redacted]

DrinkerBiddle&Reath LLP

With respect to your request regarding the Defendant's Second Set of Interrogatories, we initially stated that we did not think that the responses need clarification and that if you disagreed, you should seek relief from Court. However, in the spirit of cooperation, we will supplement our responses by Friday, March 17. We do not, however, plan to dissect deposition transcripts. Rule 33 requires that we need to specify the documents "in sufficient detail to permit the interrogating party to locate and identify, *as readily as can the party served*, the records from which the answer may be ascertained." Given that the depositions were attended by both of us, we have equal familiarity with them and it seems unnecessary to parse them for you. If you disagree, please let me know.

As for expert discovery, we agreed to stick to the Court's schedule and that we would schedule depositions after the reports had been served by the parties.

As for the depositions of John Johnson and Marcille Pilkington, we have decided that given all the other ongoing discovery and the crowded schedules of all the counsel in this case that we will forego using there testimony at trial so their depositions will not be necessary.

* * *

On an administrative note, it appears that there may have been some miscommunication between the parties regarding service. To alleviate this problem in the future, could you do us the courtesy of carbon copying David Kessler in our Philadelphia Office on all correspondence and pleadings in this action regardless to whom the letter or pleading is directed. This will ensure that we do not have any letters that are not reviewed if a lawyer is temporarily absent from his or her office. Likewise, if there is a central person, outside the primary lawyers in this action, that you want us to copy on all correspondence and pleadings, we would be happy to provide the same courtesy.

Please let me know as soon as possible if you believe I have omitted anything or inaccurately summarized our discussions.

Very truly yours,

Kathryn R. Doyle

PHLIT\555275\1

[redacted]

DrinkerBiddle&Reath LLP

Joseph R. DelMaster, Jr.
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April 3, 2006

VIA E-MAIL AND FIRST CLASS

Jeffrey M. Olson, Esq.
SIDLEY AUSTIN LLP
555 West 5th Street
Suite 4000
Los Angeles, CA 90013-1010

RE: Discovery telephone conference

Dear Jeff:

This letter is intended as a summary of our telephone conference last Thursday evening (March 30, 2006) in which we discussed several ongoing discovery matters and attempted to bring resolution to at least some of them. If you disagree with any of what follows, please let me know.

Redactions

We raised an issue (as we have in earlier correspondence) relating to redactions of documentary material that has been produced by your client(s). When we redact material from a document, the redaction is noted in the document and a reason for the redaction is provided to you in one way or another. In a large number of lawsuits, this is the first time I have seen a party redact material, or produce incomplete documents, without noting the redaction so that the extent of the withheld material can be seen and inquiries made as to the reason for the redaction. In our discussion, you referred to properly noting the redaction as "make work" and declined to correct the documents. Of course we all like to avoid useless efforts, but in the case of redacted material in otherwise responsive documents it is common practice to note the location and extent of redacted material. No agreement was reached on this issue and it may appear in any proposed stipulation describing unresolved disputes.

Cytori documents

We are not convinced that Cytori properly produced documents responsive to the subpoena. A very few documents were produced. None of them was a document described to us in a deposition three days later as having been provided to Cytori by the University of California for Olympus' benefit that addressed the invention technology and ownership of the subject intellectual property. You provided a privilege log in which certain documents that were exchanged between Cytori and Olympus prior to their closing a stock purchase agreement were noted as privileged. We disagree with that and you have agreed to rethink that designation, without commitment as to the outcome.

Established 1849

We have agreed to provide a privilege log of materials withheld to date. It will be forthcoming as soon as we have it complete.

Cytori-Olympus Joint Venture
Olympus, Inc.

We discussed the production of documents by the JV and Olympus in response to the subpoenas served on both. You have refused to provide responsive documents so far and maintain that this discovery is not going to be completed.

We have advised that motions to compel responses will be filed in the appropriate jurisdictions. You believe that the California court should rule on this dispute. We disagree and will proceed in Delaware and New York.

University of Pittsburgh documents

We believe that all responsive documents have been produced, with the exception of Dr. Llull's personal notes. Those, we are assured, have been shipped and we should have them to you shortly. Any potential document sources identified in Frances Connell's deposition are being searched and if any documents are located they will be produced.

Linda Powers

We are aware of your concern that Ms. Powers did not conduct a proper search for documents. We are taking steps to ensure that such a search is completed in the next week or so.

University of Pittsburgh witnesses

You expressed the feeling that UPitt has not attempted to locate persons who can testify with knowledge about Dr. Hedrick's relevant activities at UPitt and who can, if possible, corroborate the testimony and evidence provided by Drs. Katz, Llull and Futrell. I advised that due to high turnover we did not discover anyone to fit either of these models, but I assured you that we would make a final check and advise you of the result.

Cytori discovery

You have expressed in your correspondence a reluctance to permit discovery of Cytori because you allege that Dr. Doyle and Dr. Nguyen merely want information to enhance the patent filings for Cognate Therapeutics, Inc. I advised that nothing could be further from the truth. In fact, we do not seek anything about Cytori's technology

DrinkerBiddle&Reath LLP

developments or business enterprises, with the exception of its dealings with Olympus and, in particular, how they were advanced by information exchanges directed to the invention, the inventorship dispute, and ownership of the '231 patent. The subpoenas have all been limited to that narrow category. Though you are free to make whatever arguments you think are valid to contest discovery, that argument (that Drinker attorneys are trying to steal technology information to benefit a client) is specious and not supported by the subpoenas themselves. We cannot agree to limit legitimate discovery on this ground.

I have tried hard to accurately recount our discussion. As noted above, we still have disputes about the redaction matter and documents from Cytori, the Joint Venture, and Olympus. Those will likely be subjects of future action.

Very truly yours,

Joseph R. DelMaster, Jr.

JRD

Cc: Kathryn W. Doyle, Esq.
John J. Marshall, Esq.
George J. Awad, Esq.
David J. Kessler, Esq.
Quang Nguyen, Ph.D.
James Lewis, Esq.
Jennifer Phelps, Esq.

G

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

UNIVERSITY OF PITTSBURGH OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION, Plaintiff, vs. MARC H. HEDRICK, PROSPER BENHAIM, HERMANN PETER LORENZ, and MIN ZHU, Defendants.	CASE NO. CV:04-9014-CBM(AJWx)

C O N F I D E N T I A L

DEPOSITION OF CHRISTOPHER J. CALHOUN,

taken at 550 West C Street, Suite 2050,

San Diego, California, at 9:59 a.m.,

Friday, March 24, 2006, before Elaine

Smith, CSR No. 5421

APPEARANCES:

FOR PLAINTIFF:

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FOR DEFENDANTS:

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FOR CYTORI THERAPEUTICS:

CYTORI THERAPEUTICS
BY: RICHA NAND, ESQUIRE, IN-HOUSE COUNSEL
3020 Callan Road
San Diego, California 92121
(858)458-0900

A He's a business development director at Cytori.
Q Doug Arm.
A He's a vice president of product development engineering at Cytori.
Q Mike Schulzki.
A He was a manager in that same group. He's no longer with us. No longer with the company that is.
Q Tom Nomura?
A He's part of the Olympus team. I don't know his title.
Q Is his name Tom or something like Tomashigi?
A No. It's Tomo something.
Q Mak Hara?
A Part of the Olympus team.
Q From Japan?
A Yeah, Tokyo.
Q Nomura as well?
A Yes.
Q I have a name here, it's only an initial. H. Koyanagi.
A How do you spell it?
Q K-O-Y-A-N-A-G-I is the way I have it here.
A I don't recognize that name.
Q Nobuki Fujiwara.
A I don't recognize that name either.

Q Emiko Kato?
A I don't recognize that name.
Q Someone named K. Kouda, K-O-U-D-A.
A He's part of the Olympus team.
Q Japan?
A Yeah. I assume the other guys are too. But they have so many people I don't recognize them all.
Q Did you ever meet with anyone from Olympus America?
A Not then.
Q When?
A There is a member of the board from Olympus America.
Q Their board or your board?
A The joint venture board.
Q Who is it?
A It's -- the last name is Watanabe. W-A-T-A-N-A-B-E, I think.
Q It's like Smith in Japan, I think. I've seen that name a lot. No first name?
A I don't know his first name.
Q He's a member of the board -- that is a he?
A Yes.
Q A member of the Olympus-Cytori joint venture board of directors?

A Correct.
Q When did he first appear on the scene in your area?
A January 2006.
Q All right. Going back to the early discussions between Olympus and MacroPore, when did MacroPore become Cytori?
A June-July 2005.
Q Okay. I'll try to remember that going through our dates here. Early discussions, Olympus and MacroPore, you said a few minutes ago that their initial interest was in your biomaterials business and products.
A Correct.
Q It appears that that has changed to a principal focus in the stem cell business. Is that accurate?
A I would say the stem cell opportunity has developed fastest.
Q To the exclusion of biomaterials?
A No. We're still talking.
Q But so far there's no particular relationship based on the biomaterials product line?
A That's right, no formal relationship.
Q So when did the focus change in the early discussions from biomaterials to stem cells?
A I would say during the first meeting.

Q Was Dr. Hedrick in that meeting?
A No.
Q Who put stem cells on the table?
A I did.
Q What did you tell them?
A I just gave them a brief overview of our strategy and business model and a little bit about the technology.
Q The license?
A No.
Q At what point did your license rights -- your, I'm using the corporate your there -- the license from UC become a subject of common knowledge with Olympus between the two of you?
A I would say as the discussion sort of progressed.
Q Prior to the March initial agreement?
A I would say they were aware of it, but the due diligence that they did was after that.
Q All right. Do you recall when Dr. Hedrick may have had his first meetings with the Olympus people?
A Yeah. They came to San Diego a few weeks later, and I'm sure they met Dr. Hedrick at that time. I wouldn't say I'm sure. I would say I would expect they would have met him at that time.
Q You're not certain?
A I'm not certain. But if he were in town and

H

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

UNIVERSITY OF PITTSBURGH OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION,

Plaintiff,

vs.

MARC H. HEDRICK, PROSPER BENHAIM, HERMANN PETER LORENZ, and MIN ZHU,

Defendants.

Case No. CV:04-9014-CBM (AJWx)

Stipulation and [~~Proposed~~] Protective Order Governing Production of Documents and Other Discovery

WHEREAS, plaintiff University of Pittsburgh ("Plaintiff") has commenced the above-captioned action (the "Action") against defendants Prosper Benhaim, Marc H. Hedrick, Hermann Peter Lorenz, and Min Zhu (the Plaintiff and Defendants are hereinafter collectively referred to as the "Parties");

WHEREAS, the dispute concerns United States Patent No. 6,777,231 ("the '231 patent");

WHEREAS, there are seven named inventors of the '231 patent: the Defendants and Adam J. Katz, Ramon Llull, and William J. Futrell (collectively, the "Inventors");

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LAW OFFICES
DRINKER BIDDLE & REATH LLP
Los Angeles

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PA/521633134

WHEREAS, rights in the '231 patent have been assigned to Plaintiff and the Regents of the University of California ("Regents");

WHEREAS, the Regents have licensed certain rights in the '231 patent to Cytori Therapeutics, Inc. ("Cytori");

WHEREAS, Plaintiff has licensed certain rights in the '231 patent to Artecel Inc. ("Artecel").

WHEREAS, the Parties anticipate that discovery requests served in the Action may require the production for inspection and copying of documents containing, and testimony regarding proprietary business information of technical or financial nature, which may include trade secrets;

WHEREAS, the Parties, pursuant to Rule 26 (c) of the Federal Rules of Civil Procedure and other applicable law, believe that the entry of an Order limiting the handling and use of confidential information will facilitate their efforts to exchange documents and information with one another and to obtain documents and information from third parties to the extent necessary in this Action;

WHEREAS, the Parties desire to expedite the flow of discovery material, to facilitate the prompt resolution of disputes over confidentiality, and to ensure that protection is afforded only to material so entitled, during proceedings in this matter;

WHEREAS, the Parties seek to ensure that such confidential information is used only for purposes of this Action and is not otherwise used or disseminated; and

WHEREAS, the Parties intend to be bound by this Stipulated Protective Order (the "Order").

NOW, THEREFORE, IT IS HEREBY STIPULATED, AGREED, AND ORDERED AS FOLLOWS:

1. In the event that any documents, interrogatory answers, responses to requests for admission, depositions or other testimony, or other information or materials produced or exchanged during the course of discovery or at the trial of this Action, whether through formal or informal discovery proceedings ("DISCOVERY

MATERIAL"), are designated as being "CONFIDENTIAL" or "ATTORNEY EYES ONLY" in accordance with this Order, the designated material produced shall be maintained in confidence and not be disclosed to any person except as provided herein.

2. Material designated "CONFIDENTIAL" is non-public information concerning the conception and reduction to practice of the inventions described in the claims of the '231 patent, including trade secrets and other information that could confer a competitive advantage if publicly disclosed;

3. Material designated "ATTORNEY EYES ONLY" is other, non-public information including trade secrets and other information that could confer a competitive advantage if publicly disclosed. Such information includes, but is not limited to, non-public financial reports, licenses, licensing reports, pricing information, cost information and any relevant, non-public research information that does not concern the conception and reduction to practice of the inventions described in the claims of the '231 patent.

4. DISCOVERY MATERIAL designated as CONFIDENTIAL or ATTORNEY EYES ONLY in accordance with the terms of this Protective Order is hereinafter referred to as "PROTECTED MATERIAL."

5. Counsel for a Party or any third party producing or furnishing DISCOVERY MATERIAL (the "Producing Party") of any nature in connection with this Action to a Party (a "Receiving Party") may, except as provided in paragraph 6 below, designate a document as CONFIDENTIAL or ATTORNEY EYES ONLY by stamping each page of the document, or the portions of the document which are believed to warrant such protection, with the words "CONFIDENTIAL" or "ATTORNEY EYES ONLY," as the case may be, at the time the document is produced. PROTECTED MATERIAL not reduced to documentary, tangible or physical form or which cannot be conveniently designated in the manner set forth herein shall be designated by the Producing Party by informing the Receiving Party

in writing.

6. In the event that a Producing Party requests to designate a document as CONFIDENTIAL or ATTORNEY EYES ONLY after its initial production, the Producing Party shall also provide a replacement copy of the document marked CONFIDENTIAL or ATTORNEY EYES ONLY, and the Receiving Party shall return or destroy the corresponding unmarked document that was initially produced, along with any copies, duplicates, or extracts thereof. However, no party shall be held to be in violation of this Protective Order for the dissemination of PROTECTED MATERIAL if such material was not designated as either ATTORNEY EYES ONLY or CONFIDENTIAL at the time of the dissemination.

7. A Party may designate any deposition transcript or portion of any deposition transcript as CONFIDENTIAL or ATTORNEY EYES ONLY by so stating on the record. If the Party designates the entire transcript as CONFIDENTIAL or ATTORNEY EYES ONLY or both, the Party shall give notice in writing to the other Parties within fourteen (14) days of receipt of the deposition transcript of the pages which are so designated. Pending expiration of the fourteen (14) business days, the deposition transcript shall be treated as if it had been designated "CONFIDENTIAL." In either of the foregoing instances, the stenographer shall be instructed to place the word(s) "CONFIDENTIAL" or "ATTORNEY EYES ONLY," as appropriate, on the first page or on the designated portions of the transcript.

8. All PROTECTED MATERIAL which is produced in this Action shall be used for purposes of this Action only and for no other purpose. No person who receives PROTECTED MATERIAL from a Producing Party, or otherwise, pursuant to this Order shall disclose the PROTECTED MATERIAL to any other person, except as authorized by the express terms of this order. The Parties and all other persons who receive PROTECTED MATERIAL shall be under a continuing duty not to disclose such information obtained in the course of this Action, and this duty

shall continue in full force and effect after the completion of this Action.

9. PROTECTED MATERIAL that is designated as CONFIDENTIAL, including any writing or communication reproducing, paraphrasing, or otherwise disclosing such information, shall not be shown or disclosed to any person by the Receiving Party except to the following persons:

(a) The outside attorneys of record for the Parties, including the partners, associates, and stenographic, secretarial, paralegal, clerical and other employees of such attorneys;

(b) The Inventors;

(c) Alan A. Garfinkel, Francis Connell, and Mark Melandro of the University of Pittsburgh; Ken Mosely and Linda Powers of Artecel; Martin Simpson, Patricia Cotton, John Shih, Bernadette McCafferty and Kathryn Atchison of the Regents, Richa Nand and Jon Soneff of Macropore, and any similarly-situated persons agreed to in a writing signed by each of the Parties' outside counsel;

(d) Independent consultants or expert witnesses ("Independent Experts") retained by such Party, including the partners, associates, and stenographic, secretarial, paralegal, clerical and other employees of such Independent Experts. Before disclosing any materials marked CONFIDENTIAL to an Independent Expert, counsel shall provide to the other Parties a copy of a resume or curriculum vitae describing in detail: (1) the Independent Expert's employment history; and (2) every consulting relationship in which the Independent Expert is currently engaged or has been engaged in the past four years. The notified Parties shall have ten (10) business days from receipt of the notice to deliver to the notifying party written objections, if any, setting forth in detail the reasons therefor. Upon timely objection, disclosure of materials marked CONFIDENTIAL to the Independent Expert shall not be made, subject to a successful motion for relief brought by the Party seeking disclosure. Absent timely objection, the Independent Expert shall be deemed approved.

SO AMENDED

(e) Any person who prepared or originated the document, or who is indicated on its face as a recipient of a copy thereof;

(f) The Court and related officials involved in this Action, including judges, magistrates, commissioners, referees, jurors, and other Court personnel; provided, however, that any material designated CONFIDENTIAL and filed with Court is served and filed in accordance with the procedures for the service and filing of such material contained in this Order.

(g) Any person designated by the Court in the interest of justice, upon such terms as the Court deems proper.

10. Prior to disclosing CONFIDENTIAL material to any person listed in paragraphs 9(b), 9(c), 9(d) 9(e) and 9(g) above, the Receiving Party shall provide such person with a copy of this Order and obtain from such person a signed copy of the Certificate of Compliance With Protective Order ("Certificate") in the form attached hereto as Exhibit "A." Such statement shall be retained by the Receiving Party and need not be filed with the Court or served upon opposing counsel unless required by the Court.

11. PROTECTED MATERIAL that is designated as ATTORNEY EYES ONLY, including any writing or communication reproducing, paraphrasing, or otherwise disclosing such information, shall not be shown or disclosed by the Receiving Party except to the following persons:

(a) The outside attorneys of record for the Parties, including the partners, associates, and stenographic, secretarial, paralegal, clerical and other employees of such attorneys;

(b) Alan A. Garfinkel of the University of Pittsburgh and Martin Simpson of the Regents;

(c) Independent Experts retained by such Party, including the partners, associates, and stenographic, secretarial, paralegal, clerical and other employees of such Independent Experts. Before disclosing any materials marked

CONFIDENTIAL to an Independent Expert, counsel shall provide to the other Parties a copy of a resume or curriculum vitae describing in detail: (1) the Independent Expert's employment history; and (2) every consulting relationship in which the Independent Expert is currently engaged or has been engaged in the past four years. The notified Parties shall have ten (10) business days from receipt of the notice to deliver to the notifying party written objections, if any, setting forth in detail the reasons therefor. Upon timely objection, disclosure of materials marked CONFIDENTIAL to the Independent Expert shall not be made, subject to a successful motion for relief brought by the Party seeking disclosure. Absent timely objection, the Independent Expert shall be deemed approved.

(d) Any person who prepared or originated the document, or who is indicated on its face as a recipient of a copy thereof;

(e) The Court and related officials involved in this Action, including judges, magistrates, commissioners, referees, jurors, and other Court personnel; provided, however, that any material designated ATTORNEY EYES ONLY and filed with the Court is served and filed in accordance with the procedures for the service and filing of such material contained in this Order; and

(f) Any person designated by the Court in the interest of justice, upon such terms as the Court deems proper.

12. Prior to disclosing ATTORNEY EYES ONLY material to any person listed in paragraphs 11(b), 11(c), 11(d) and 11(f) above, the Receiving Party shall provide such person with a copy of this Order and obtain from such person a signed copy of the Certificate in the form attached hereto. Such statement shall be retained by the Receiving Party and need not be filed with the Court or served upon opposing counsel unless required by the Court.

13. If counsel for a Receiving Party in good faith objects to the designation by the Producing Party of PROTECTED MATERIAL as ATTORNEY EYES ONLY or CONFIDENTIAL, counsel for the Receiving Party must state the

objection in writing and provide such written objection to the Producing Party as soon after the Receiving Party believes there is a good-faith basis for such objection, but in any event not later than thirty (30) days before the deadline to file discovery motions. If no written notice of objection is received within this period, the Receiving Party shall be deemed to have waived any right to object to the designation The notice of objection shall identify the PROTECTED MATERIAL subject to the objection, set forth the reasons and bases for the objection, and if applicable identify the person to whom the Receiving Party wants to disclose the PROTECTED MATERIAL. If timely written notice of objection is provided, the Parties shall, within seven (7) days, meet and confer in good faith in an attempt to informally resolve the dispute over the designation. If they are unable to resolve the disagreement, the Producing Party shall move the Court for a protective order to maintain the designation of the PROTECTED MATERIAL, and shall bear the burden of proving good cause for the designation.

14. ~~In the event that~~ any Party seeking to file ~~in connection with any motion or proceeding~~ ~~files~~ with the Court any records that disclose the contents of PROTECTED MATERIAL, must comply with local Rule 79-5.1 and submit a written application, ~~these records shall be filed with the Court in sealed envelopes on~~ including legal authority for such application, and a proposed order to the judge, ~~which a captioned page shall be taped that states: "FILED UNDER SEAL — PURSUANT TO PROTECTIVE ORDER."~~ along with the documents submitted for filing, under seal. In addition, separate versions of those documents, captioned "PUBLIC REDACTED VERSION," shall be filed concurrently in the Court's public files. In the PUBLIC REDACTED VERSION of the filed records, PROTECTED MATERIALS shall be replaced with a sheet or sheets stating words to the effect that the PROTECTED MATERIALS were not included pursuant to this Order. In addition, in the PUBLIC REDACTED VERSION of the filed records, references to PROTECTED MATERIALS shall be redacted, and each such redacted page shall be stamped "REDACTED."

15. Should any PROTECTED MATERIAL be disclosed, through inadvertence or otherwise, by the Receiving Party to any person not authorized under this Order, the Receiving Party shall:

(a) Within two (2) business days of the discovery of such disclosure, inform the recipient of such PROTECTED MATERIAL of all provisions of this Order and use its best efforts to obtain the return of such PROTECTED MATERIAL and to have such person sign the Certificate attached to this Order. The executed Certificate shall be served upon counsel of record for the Producing Party within five (5) days of its receipt by the Receiving Party; and

(b) Within two (2) days of the discovery of such disclosure, provide a written explanation to the Producing Party describing the PROTECTED MATERIAL that was disclosed, explaining the reason for the disclosure, and identifying the person to whom it was disclosed.

16. The restrictions set forth in this Order shall not apply to any document or other information that was properly in the public domain or was acquired in good faith from a third party. In the event a Party claims that one or more documents was improperly put in the public domain, the Party shall seek to resolve the issue informally through negotiation. If that does not resolve the issue, a Party may move the Court for an Order directing that said document(s) is/are subject to this Order. Nothing herein shall prevent any of the Parties from disclosing or using any of their own PROTECTED MATERIAL as they deem appropriate.

17. Any Party who has designated any material as ATTORNEY EYES ONLY or CONFIDENTIAL pursuant to this Order may consent to the removal of such designation by so notifying counsel for the other Party in writing.

18. Nothing in this Order shall be construed to preclude or to constitute a waiver of any Party's right: (a) to oppose discovery on any ground; (b) to object on any ground to the admission into evidence of any document, testimony, evidence, or other information at the trial of this Action; or (c) to seek an order from the Court

that any portion of a hearing or trial proceeding be closed to the public for the purpose of taking testimony with respect to information designated as PROTECTED MATERIAL. Nothing herein shall affect, impact or change in any way the protections afforded by any applicable privilege, including, but not limited to, the attorney-client privilege and work product protection or their inadvertent disclosure.

19. This Stipulation shall be, subject to the Court's approval, binding upon all of the Parties upon their signature hereto, and by signing hereto each Party agrees to comply with the terms of this Stipulation and to be bound thereby. In the event that the Court does not enter into the Proposed Protective Order based upon this Stipulation, the Parties shall in good faith negotiate the terms which the Court finds objectionable.

20. Any additional Party who joins or is joined in this Action shall have access to PROTECTED MATERIAL in accordance with the provisions of this Order upon its counsel's executing and filing with the Court a declaration in which the Party and its counsel agree to be fully bound by this Order.

21. Within thirty (30) days after the termination of this Action, including any appeals, or at such other time as the Parties agree, each Party shall return or destroy all documents containing or reflecting PROTECTED MATERIAL, including, but not limited to, originals, copies, and excerpts of PROTECTED MATERIAL. Each Party shall serve on all other Parties a signed letter confirming that it complied with this provision of the Protective Order by returning or destroying all PROTECTED MATERIAL received from other Parties. Notwithstanding the foregoing, counsel for each Party may retain their work product, such as pleadings, correspondence, and memoranda which contain or reflect PROTECTED MATERIAL, provided that all such information shall remain subject to this Order and shall not be disclosed to any person except as provided by this Order.

22. This Order shall not prejudice a Party's right to seek to amend, modify, or change the terms of Order by written agreement between the Parties (and relevant third parties, to the extent that their interests are affected), or by Order of the Court.

23. In the event that a Party or entity who has received PROTECTED MATERIAL in connection with this Action is (a) subpoenaed in another action, (b) served with a demand in another action to which he, she or it is a party, or (c) served with any other legal process by one who is not a Party to this Action, and the subpoena, demand, or other legal process calls for the production of PROTECTED MATERIAL, the Receiving Party shall, within at least forty-eight (48) hours of receiving said subpoena, demand, or legal process (or sooner if the time for responding is less than forty-eight (48) hours), provide the Producing Party by email or facsimile transmission with written notice and a copy of said subpoena, demand, or legal process in order to allow the Producing Party to quash or modify said subpoena, demand, or legal process.

24. The Parties agree that a violation or threatened violation of these terms shall constitute irreparable harm and qualify as valid grounds for seeking injunctive relief to prevent said violation.

25. This Order governs the use and handling of PROTECTED MATERIALS prior to trial. Before trial, the Parties shall meet and confer to discuss the procedures to be used at trial to maintain the confidentiality of PROTECTED MATERIALS in a manner consistent with the Court's Rules and procedures.

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IT IS SO ORDERED.

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DATED 12/6/05

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UNITED STATES DISTRICT JUDGE

///

IT IS SO STIPULATED.

DATED: November 23, 2005

DRINKER BIDDLE & REATH LLP

By: John J. Marshall
John J. Marshall
Amor A. Esteban
Suzanne V. Stouder
Attorneys for Plaintiff
University of Pittsburgh

DATED: November 21, 2005

BINGHAM McCUTCHEN

By: _____
James B. Lewis
Thomas E. Kuhnle
Malcolm McGowan
Jennifer M. Phelps
Attorneys for Defendants

DATED: November __, 2005

SIDLEY AUSTIN BROWN & WOOD

By: _____
Jeffrey M. Olson
Sandra S. Fujiyama
Attorneys for Defendant
Marc H. Herick

SCANNED

IT IS SO STIPULATED.

DATED: November ___, 2005

DRINKER BIDDLE & REATH LLP

By: _____
John J. Marshall
Amor A. Esteban
Suzanne V. Stouder
Attorneys for Plaintiff
University of Pittsburgh

DATED: November 21, 2005

BINGHAM McCUTCHEN

By: Jennifer M. Phelps
James B. Lewis
Thomas E. Kuhnle
Malcolm McGowan
Jennifer M. Phelps
Attorneys for Defendants

DATED: November __, 2005

SIDLEY AUSTIN BROWN & WOOD

By: _____
Jeffrey M. Olson
Sandra S. Fujiyama
Attorneys for Defendant
Marc H. Herick

IT IS SO STIPULATED.

DATED: November ___, 2005

DRINKER BIDDLE & REATH LLP

By: _____
John J. Marshall
Amor A. Esteban
Suzanne V. Stouder
Attorneys for Plaintiff
University of Pittsburgh

DATED: November 21, 2005

BINGHAM McCUTCHEN

By: _____
James B. Lewis
Thomas E. Kuhnle
Malcolm McGowan
Jennifer M. Phelps
Attorneys for Defendants

DATED: November 21, 2005

SIDLEY AUSTIN BROWN & WOOD

By: /s/ [illegible]
Jeffrey M. Olson
Sandra S. Fujiyama
Attorneys for Defendant
Marc H. Herick

SCANNED

ORDER

For GOOD CAUSE APPEARING, it is SO ORDERED.

DATED: _____, 2005

The Honorable Consuelo B. Marshall
Chief District Judge

ENTERED

EXHIBIT "A"

CERTIFICATE OF COMPLIANCE WITH PROTECTIVE ORDER

The undersigned declares as follows:

I hereby acknowledge that I have been provided with a copy of the Stipulation and Order Governing Production of Other Discovery of ATTORNEY EYES ONLY Information (the "Protective Order") in the action captioned *University of Pittsburgh, etc. v. Marc H. Hedrick, et al.*, United States District Court (Central District), Case No. CV-04-9014-CBM (AJWx).

I agree to abide by the Protective Order and not to reveal or otherwise communicate to anyone or utilize any of the information designated "ATTORNEY EYES ONLY" or "CONFIDENTIAL" that is disclosed to me except in accordance with the terms of such Order. I acknowledge that any violation of the Protective Order may be punishable as to contempt of court through monetary sanctions ordered by the Court , or both, and I further agree to submit to the jurisdiction of the United States District Court (Central District) for all matters relative to such Order.

DATED: _____, ____

_____
(Signature)

_____
(Printed Name)

_____
(Address)

PROOF OF SERVICE

I am over 18 years of age, not a party to this action and employed in the County of Los Angeles, CA at 355 South Grand Avenue, Suite 4400, Los Angeles, CA 90071-3106. I am readily familiar with the practice of this office for collection and processing of correspondence for mailing with the United States Postal Service and correspondence is deposited with the United States Postal Service that same day in the ordinary course of business.

Today I served the attached:

STIPULATION AND [PROPOSED] PROTECTIVE ORDER GOVERNING PRODUCTION OF DOCUMENTS AND OTHER DISCOVERY

by causing a true and correct copy of the above to be placed in the United States Mail at Los Angeles, CA in sealed envelope(s) with postage prepaid, addressed as follows:

Amor A. Esteban, Esq.
Drinker Biddle & Reath LLP
333 South Grand Avenue, Suite 1700
Los Angeles, CA 90071-1504
Phone: 213-253-2300
Fax: 213-253-2301
Attorneys for Plaintiff

Jeffrey M. Olson, Esq.
Sidley Austin Brown & Wood LLP
555 West 5th Street, 40th Floor
Los Angeles, CA 90013
Phone: 213-896-6041
Fax: 213-896-6600
Attorneys for Defendant Marc H. Hedrick

I declare that I am employed in the office of a member of the bar of this court at whose direction the service was made and that this declaration was executed on December 1, 2005.

Nancy J. Phillips

* *UNEDITED REALTIME TRANSCRIPT - NOT CERTIFIED * *

THIS IS A REALTIME ROUGH DRAFT TRANSCRIPT. IT IS NOT CERTIFIED BY THE DEPOSITION OFFICER, PURSUANT TO CCP SECTION 2025(R)(2), IT MAY NOT BE USED, CITED, OR TRANSCRIBED AS THE CERTIFIED TRANSCRIPT OF THE DEPOSITION PROCEEDINGS. THE ROUGH DRAFT TRANSCRIPT MAY NOT BE CITED OR USED IN ANY WAY OR AT ANY TIME TO REBUT OR CONTRADICT THE CERTIFIED TRANSCRIPT OF THE DEPOSITION PROCEEDINGS AS PROVIDED BY THE DEPOSITION OFFICER.

BY ACCEPTING A ROUGH DRAFT TRANSCRIPT, I AM ORDERING A FINAL CERTIFIED TRANSCRIPT. I AGREE NOT TO SHARE, GIVE, COPY, SCAN, FAX, OR IN ANY WAY DISTRIBUTE THE REALTIME ROUGH DRAFT IN ANY FORM (WRITTEN OR COMPUTERIZED) TO ANY PARTY. HOWEVER, MY OWN EXPERTS, CO-COUNSEL, CLIENT(S) AND STAFF MAY HAVE LIMITED INTERNAL USE OF SAME WITH THE UNDERSTANDING THAT I AGREE TO DESTROY ALL REALTIME ROUGH DRAFTS AND/OR COMPUTERIZED FORMS, IF ANY, AND REPLACE SAME WITH THE FINAL TRANSCRIPT AND/OR FINAL COMPUTERIZED FORM, UPON ITS COMPLETION.

WHOLE TX. CONFIDENTIAL

San Francisco, California

Monday, March 27, 2006

9:59 a.m. - 5:31 p.m.

BY MR. DELMASTER:

Q If -- I'm going to say what I've heard -- the way I've heard your name pronounced. Mr. Shih? Shih?

A Shih.

Q Shih?

A Yes.

Q Thank you.

I'm Joseph Delmaster. I represent the University of Pittsburgh in this litigation.

Now, the first thing I'm going to ask you is, have you ever done this before, had a deposition taken?

A Yes, I have.

Q Okay. Then I'll skip the long-winded instructions and just confirm that you understand that the testimony that you're giving today -- you've just been sworn obviously to be truthful -- can be used in a trial of this case if it comes to that. Do you understand that?

A Yes, I do.

Q Now, when I say this case, are you familiar with the litigation, at least the general subject matter of the litigation between the University of Pittsburgh and the persons who are named as the inventor on what we called the '231 patent?

Q Dealings with Mac report bio surgery connected with the '231 patent?
A Yes.
Q And also Cytori Therapeutics?
A Yes.
Q Do you know who Marc Hedrick is?
A Yes, I do.
Q Did you have personal dealings with Mr. Hedrick?
A What do you mean by personal,
Q Relating to the '231 patent or related invention disclosures to the university and their processing?
A Yes.
Q Can you speak for the university regarding the technology transfer and licensing activity about the '231 patent?
A Yes.
Q Do you have any knowledge about an investment in Cytori bio Olympus corporation and any diligence exercises that Olympus may have done that involved the university? In other words, inquiries from the Olympus about the inventorship of the'231 patent or any of the --
A I am aware of Olympus's interest in this patent. I cannot speak for Olympus in terms of what diligence they have performed on the subject matter.

Q Okay. Did -- do you know whether or not the university was contacted by Olympus to make any inquiries about the invention disclosure, the correct inventorship designation, or anything else related to the '231 patent or the intellectual property of Cytori?

A I am aware that Olympus did inquire and had questions concerning the intellectual properties held by Macropore. I do not have personal knowledge or any knowledge regarding their inquiries concerning inventorship.

Q But they did make some inquiry, you did know that?

A They made general inquiries to Macropore, Cytori.

Q Okay. Well, while that's in your mind, do you know who fielded those inquiries?

A No, I do not.

Q Do you know if they were written?

A No, I do not.

Q How do you know about inquiries from Olympus?

A From Macropore?

Q From Macropore.

A Yes.

Q Let me see if I got this straight. You're aware from Macropore that Olympus made some inquiry of the

university about the subject matter of the '231 patent and/or -- and/or Cytori intellectual property?

A You put it in an interesting way. Perhaps I can clarify that point.

Q Please do.

A I understood Olympus inquired, made a number of inquiries and their conversations were with Macropore. Macropore communicated Olympus's interest to the Office of Technology Transfer. So the inquiry from Olympus was indirect.

Q I see. Were you the Office of Technology Transfer at that time?

A I was the licensing officer manage this case for the Office of Technology Transfer.

Q Were you asked to respond to Macropore?

A No one actually asked me to respond to Macropore. It was my responsibility to address any concerns that Macropore may have raised.

Q Okay. Do you recall the inquiry, the specific nature? What did they want to know?

MR. LEWIS: Objection; vague.

THE WITNESS: What did they want to know? The one issue that I recall was, one, to verify that Macropore was in fact our licensee, and two, to verify that they were licensees in good standing.

Q Verify to whom?
A In a note to Macropore.
Q Did you understand that that information was to be passed on to Olympus?
A Yes.
Q Do you recall at least to the best of your recollection when this occurred?
A Within the four years. No more specific than that, no.
Q Was it a singular inquiry or was it -- did it evolve over time and become a continuing subject?
A There could have been more than one correspondence on the subject matter, but I recall it as a single event.
Q We'll see if it falls out of all the paper that we have here.
A second subpoena was served on the university for documents related to the invention that's the subject matter of this litigation and to any disclosures made by the inventors and any communications with the inventors. Rather than go down the list of documents, were you asked to participate in a document search preparatory to this deposition?
A I was asked to participate in a part of the document search in preparation for this deposition.

A At one point I would have said yes, but it is much less clear now. Different branches of government have different ideas as to what is proper for them to do with this technology.

Q Let me ask you, if the claims of the '231 patent -- this is a hypothetical, but if the claims of the '231 patent were determined to be solely the property of the University of Pittsburgh --

A Mm-hmm.

Q -- does that have an impact on University of California's expectations under it's license agreement to StemSource?

A No. We were clear with StemSource that inventorship and ownership of the patent and claims are not yet defined. So they've been put on notice that that can happen.

Q How about from a revenue standpoint? For instance, would you be concerned that StemSource -- we should call them by their current name Cytori.

Would you be concerned that Cytori could not commercialize the stem cell tissue re general tiff therapy that they have in mind if the '231 patent was in other hands?

A No. Then somebody else is going to commercialize that, and that's fine with us.

Q Would you be concerned that for instance University of Pittsburgh would enforce the '231 patent against StemSource to try to prevent it from commercializing the technology?

A Go ahead. I got no problem with that.

Q That doesn't bother the university?

A No.

Q In theory, the licensed revenues and whatever to come later would be at least temporarily cut off?

A No, not at all. The revenues that we generate from technologies such as these is next to nothing compared to the overall portfolio.

Q Meaning the entire university portfolio?

A Just UC o p. Just the main office. And it won't even make a dent. so it's really not a concern.

Q We talked a long time ago this morning about Olympus and its investment in Cytori?

A Yes.

Q Did UC have any role to play or any say in the matter?

A No. Aside from affirming that Cytori is our licensee and they're in good standing, no.

Q Were you contacted individually by Olympus or its representatives?

A Individually, no.

Q In your official capacity?
A In my official capacity, no.
Q Was the confirmation about ownership or the license agreement, whatever it was that was transmitted to Olympus done by somebody else?
A What information Olympus received concerning the license patent went from Cytori to Olympus, not from the main office, not from OTT to Olympus. If we send anything at all, we normally just send a one-page letter confirming that Cytori is our licensee, and that really is a letter we sent to Cytori, not to Olympus.
Q Let me get this straight. I've been involved in issues like this before. Is it the case that Cytori would send a request to the university to have a confirming letter sent to them?
A That is correct.
Q And then they could pass that letter on to others?
A That is correct.
Q Is it your belief then there was no direct contact between the university at Olympus?
A There was contact between the University and Olympus, not through the Office of Technology Transfer.
Q Where?
A I understand that firstly, Marc as a faculty

member, secondly, I understood that he took Olympus representatives around campus, harassing people for data. And I found out about it when some people contacted me because they felt harassed.

Q Looking for what kind of data?

A Data relating to fat derived stem cells.

Q So people involved in the research project?

A People involved in some research projects, yes.

Q Do you know who the people were who complained about being harassed as you put it?

A One of my other inventors.

Q Who is that?

A Is it -- I guess it is in the public domain at least on websites, who these people are.

MR. DELMASTER: I can't imagine that it's privileged in any way.

MR. LEWIS: Would you mind if I confer on the privilege issue.

MR. DELMASTER: Go ahead. Sure.

THE WITNESS: Just to be sure.

(Recess taken: 5:22 until 5 23

A So in answer to your question the faculty member that communicated to me that she was harassed by Marc Hedrick and a bunch of Olympus people her name was Larrisa Rodriguez.

CERTIFICATE OF SERVICE BY ELECTRONIC MAIL

On April 12, 2006, I served on interested parties in said action the within:

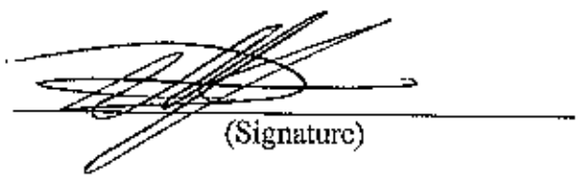
PLAINTIFF'S NOTICE OF MOTION AND MOTION TO COMPEL RESPONSES TO ITS SUBPOENA DUCES TECUM ON THIRD-PARTIES OLYMPUS CORPORATION AND OLYMPUS AMERICA INC.

by transmitting a true copy of said document by electronic mail and by United States First Class Mail as stated on the attached service list.

Executed on April 12, 2006, at Philadelphia, PA.

I declare under penalty of perjury under the laws of the State of Pennsylvania that the foregoing is true and correct.

David J. Kessler
(Type or print name)



(Signature)

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